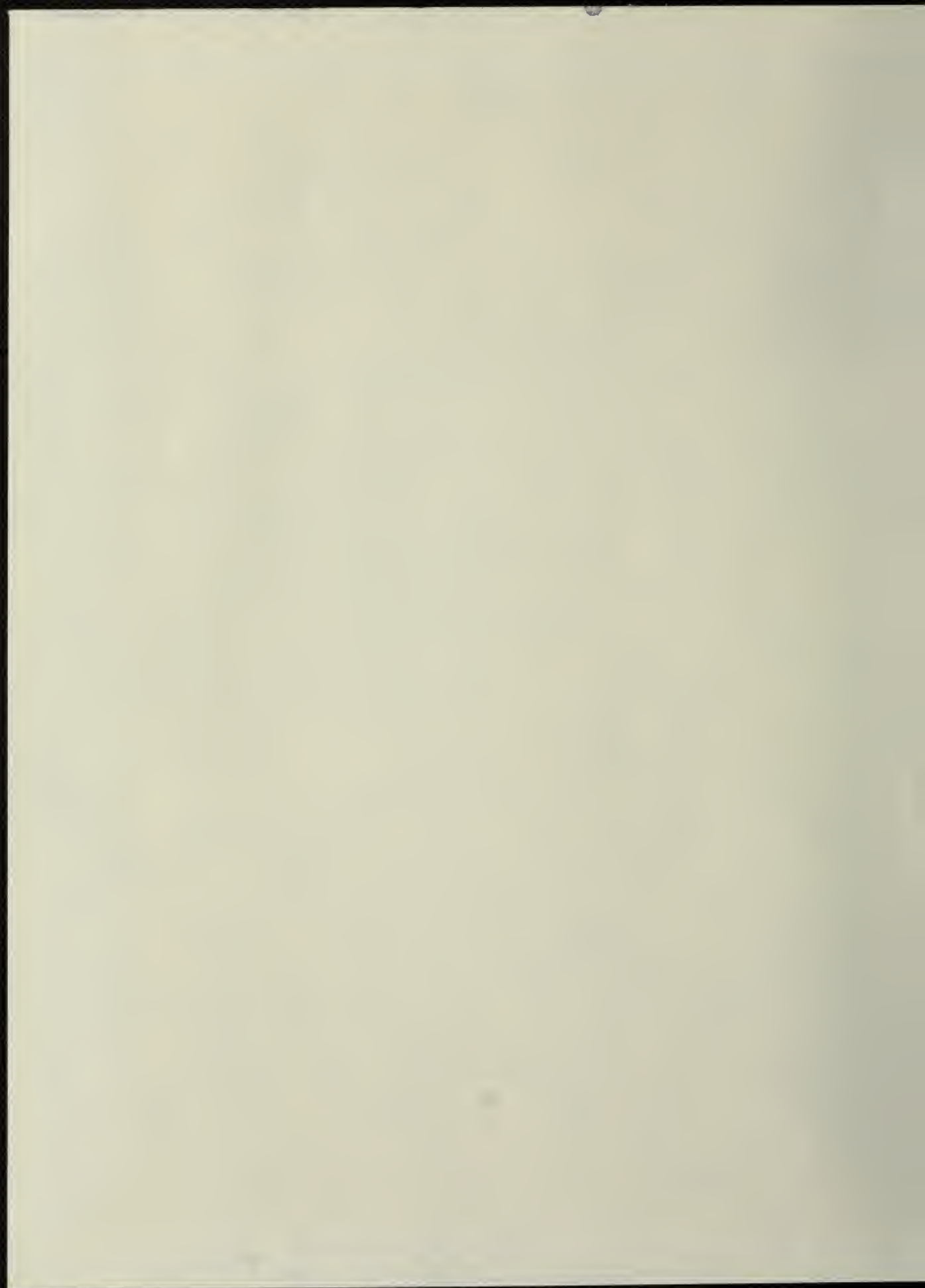


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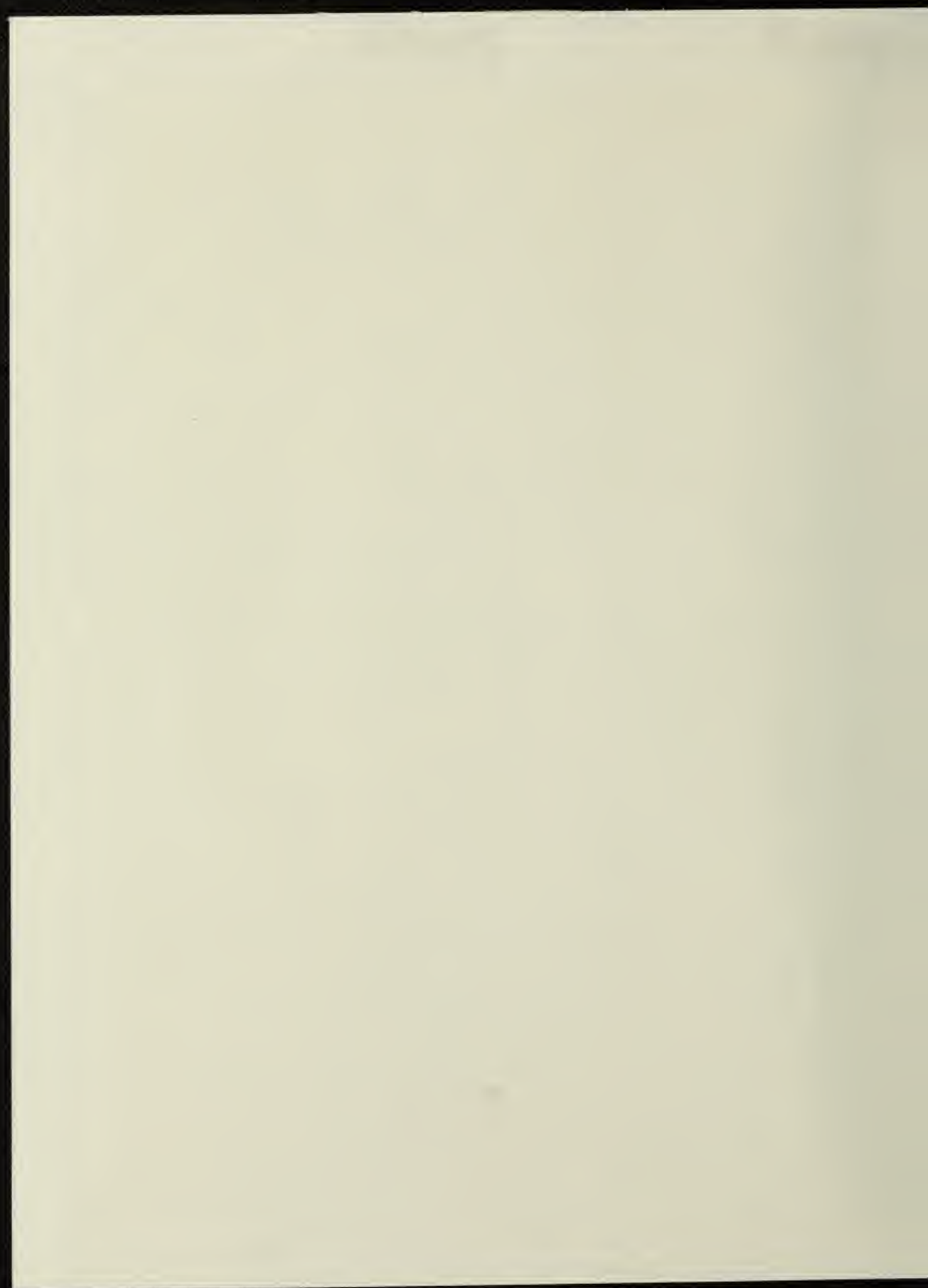
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CARCINOGENESIS ABSTRACTS

VOLUME 17, ISSUE 9

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page Nos.
REVIEW	(Rev)	79-4801—79-4939	1925
CHEMICAL CARCINOGENESIS	(Chem)	79-4940—79-5095	1956
PHYSICAL CARCINOGENESIS	(Phys)	79-5096—79-5114	1992
VIRAL CARCINOGENESIS	(Viral)	79-5115—79-5233	1997
IMMUNOLOGY	(Immun)	79-5234—79-5281	2027
PATHOGENESIS	(Path)	79-5282—79-5352	2040
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	79-5353—79-5390	2055
MISCELLANEOUS	(Misc)	79-5391—79-5400	2064
AUTHOR INDEX			2067
SUBJECT INDEX			2077
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2153
WISWESSER LINE NOTATION INDEX			2157

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ABBREVIATIONS

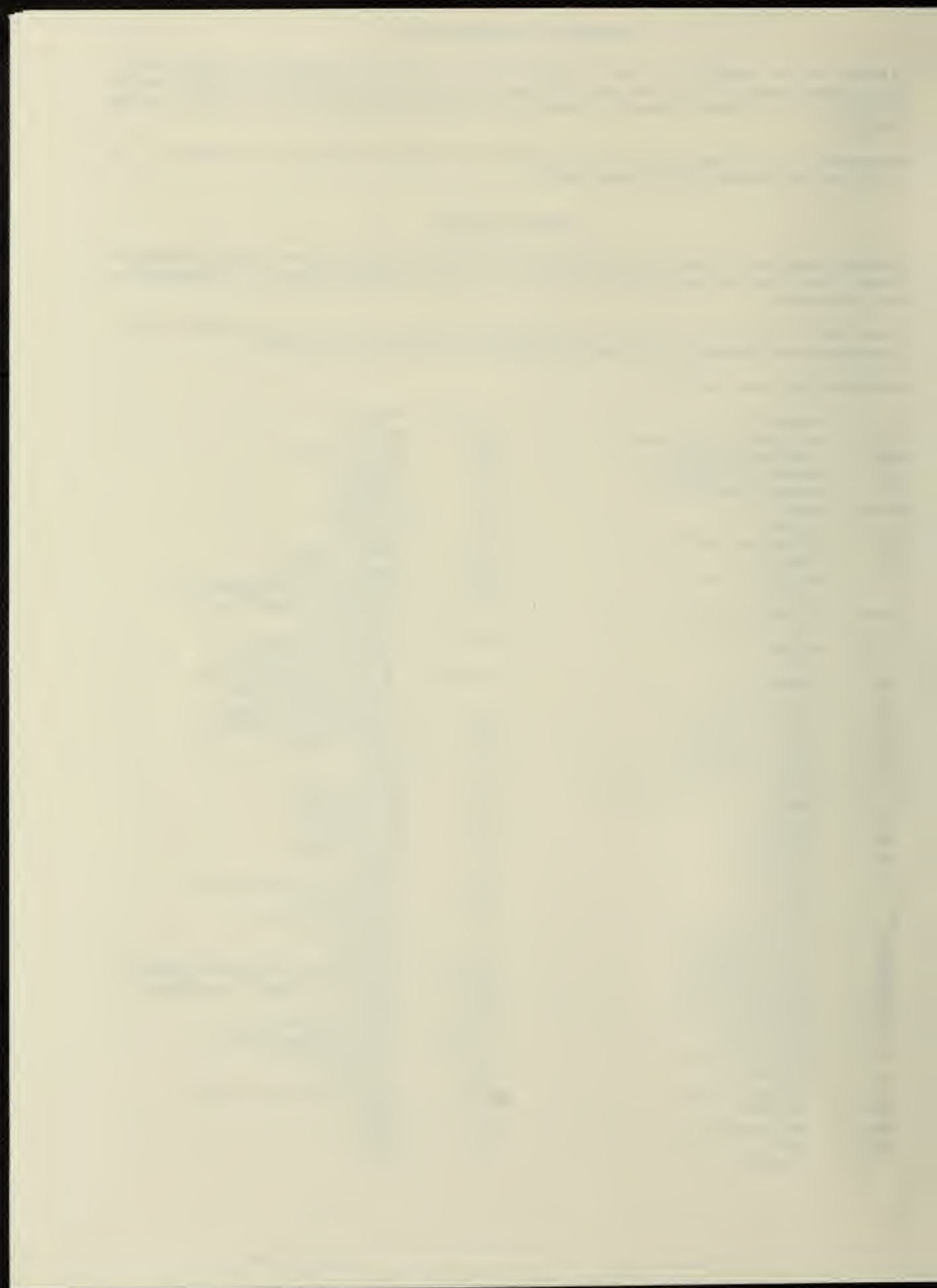
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ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		

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REVIEW

- 79-4801 ICPEMC Publication No. 2. Advice on Screening of Chemicals for Mutagenicity. (Eng) Matter, B. (Verte Rive, Lausanne, Switzerland); Kilbey, B. J.; Drake, J.; Hollaender, A.; Ramel, C.; Ray, V.; Sundaram, K. *Mutat Res* 64(3): 155-158; 1979.

Available screening tests for gene mutations include systems involving bacteria, fungi, drosophila, and cultured mammalian cells. In vivo or in vitro cytogenetics, the micronucleus test, and the dominant lethal test are used to detect chromosome damage, and evidence for primary DNA damage is obtained from bacterial repair tests, DNA repair tests in mammals, and assays for sister-chromatid exchanges, gene conversion, and mitotic recombination. The two main limitations of screening tests are the restricted spectrum of genetic damage any one test can detect and the failure of some systems to provide for metabolic conversion of compounds. (4 refs)

- 79-4802 Quantum Studies Probe Biological Molecules. (Eng) Rawls, R. L. (No affiliation given.) *Chem Eng News* 57(27): 20-21; 1979.

Improved methods for ab initio quantum mechanics provide chemists with clues to the reactivity of drugs, carcinogens, teratogens, and some biomolecules. Families of potential carcinogens, such as the benzopyrenes, are being studied to determine a structural property or set of properties that will indicate carcinogenic activity. One scientist is comparing the properties of molecules in benzopyrenes as they are metabolized to proximate and ultimate carcinogens. (no refs)

- 79-4803 Carcinogenicity Testing for Control of Environmental Tumor Development in Man. (Eng) Berenblum, I. (Weizmann Inst. Science, Rehovot, Israel). *Isr J Med Sci* 15(6): 473-479; 1979.

Rather than waiting until a new form of environmental cancer becomes clinically recognized before trying to determine its cause, high priority is now given to routine carcinogenicity testing of the various products to which humans are exposed. Carcinogenicity tests carried out in vivo are time-consuming and technically very demanding. To be reliable, these tests require an elaborate set of conditions. Short-term tests were devised primarily for preliminary screening and, possibly, to replace the laborious animal tests. Although the Ames mutagenicity

assay is not ideal, it is 90% accurate and is a notable advance in the search for rapid screening of large numbers of compounds. In this assay, the mammalian liver extract does not necessarily contain the appropriate enzyme system for all classes of carcinogens. The in vitro transformation of mammalian cells seems promising, but it needs further refinement and trials before it can be put to practical use as a routine method of carcinogenicity testing. There are several difficulties inherent in extrapolating from the results of experimental tests to humans. Apart from the problem of false positives and false negatives, there are difficulties of interpretation. This is due to differences in species, strain, organ response, etc, and also to the fact that carcinogenesis is a multistage process and subject to strong influences by cocarcinogenic factors. These factors include precarcinogens, oncogenic viruses, promoting agents, and miscellaneous factors operating in conjunction with suboptimal doses of physical, chemical, or viral carcinogens. Additional procedures are needed to detect these associated factors. (29 refs)

- 79-4804 Recommendations on Data Production and Analysis Using the Salmonella/Microsome Mutagenicity Assay. (Eng) de Serres, F. J. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Shelby, M. D. *Mutat Res* 64(3): 159-165; 1979.

Points and components of the protocol for the Ames Salmonella/microsome plate assay that could contribute to variations in results are emphasized, and recommendations are made as to where and how the protocol should be modified for use in routine mutagenicity testing. Problems in data presentation and analysis were also addressed. (3 refs)

- 79-4805 An Overview of the Problem of Thresholds for Chemical Carcinogens. (Eng) Truhaut, R. (Faculte des Sciences Pharmaceutiques, 4 Avenue de l'Observatoire, 75006 Paris, France). *IARC Sci Publ* (25): 191-202; 1979.

According to a current view, it is impossible to establish safe levels for carcinogens, because there are no thresholds for their action. This concept is supported by the arguments that (1) cancer may result from a mutation in a somatic cell; (2) the cancer cell is self-replicating; (3) with some carcinogens, the primary carcinogenic effects of any

individual dose persist and remain irreversible during the life-span of the animals, finally resulting in a tumor; (4) a lasting change is induced by one tumor-initiating event; and (5) cancer can occur in response to chemicals, even in single doses, long after their disappearance from the body. Arguments against this theory include the following: (1) every organism has a limited life-span, and, thus, has a real threshold; (2) the probability of a carcinogen reaching a single cell is lowered with minute doses; (3) a carcinogen-induced alteration of a molecular target can be repaired; (4) there is a difference between malignant cellular transformation (first stage of malignancy) and the clonal development of a transformed cell, which produces a cancer; clonal development is affected by certain host-defense reactions, and the threshold may result from what happens at that stage; (5) certain chemically induced tumors induce immunological, tumor-associated rejection reactions; (6) epidemiological studies indicate the existence of a threshold for certain exogenous carcinogenic factors (ie, cigarette smoking); (7) experimental studies indicate that thresholds exist for various carcinogens; and (8) some carcinogens give rise to tumors only after inducing particular pathologic changes. No-effect levels should be determined by long-term investigations of the effects of low levels in animals similar to humans in their metabolic potential and sensitivity. Human exposure to all chemical carcinogens should be reduced to the feasible minimum. (27 refs)

- 79-4806 The Role of Laboratory Animal Studies in Estimating Carcinogenic Risks for Man. (Eng) Rall, D. P. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709). *IARC Sci Publ* (25): 179-189; 1979.

Data from the first 16 volumes of the International Agency for Research on Cancer monograph series are analyzed in order to determine the extent to which biological responses to chemicals in laboratory animals predict those in humans. It has been shown that if there is strong evidence that a chemical is carcinogenic in appropriate laboratory animals, it must be treated as if it were carcinogenic in humans. Further evidence supporting this conclusion is presented. According to data in the monographs, there is considerable evidence that chemicals that are carcinogenic in laboratory animals are carcinogenic in humans, providing qualitative predictability, and there is tentative evidence of a quantitative relationship between the amount of a chemical that is carcinogenic in animals and the amount that is carcinogenic in humans. (3 refs)

- 79-4807 Statement Regarding OSHA's Proposed Federal Cancer Policy. (Eng) Jukes, T. H. (Div. Medical Physics, Univ. California, Berkeley, CA 94720). *Clin Toxicol* 14(1): 133-139; 1979.

The proposed Occupational Safety and Health Administration (OSHA) Federal Cancer Policy is reviewed and its validity discussed. The Policy is considered unscientific and unworkable. The 'no-threshold' concept, extending to single molecules, is biologically unsound, as is the rationale for disposing of the list of 'natural' carcinogens. The OSHA Statement ignores the concept of time as it relates to the dose-response relationship of carcinogens, as well as the concept of probability. The validity of testing for human carcinogens in experimental animals is also questionable. It is necessary to know, rather than guess, that a mouse test will positively identify a substance as a human, and not just a rodent, carcinogen. The cancer hazard for occupational exposure to 'industrial' carcinogens would be considerably reduced by the elimination of cigarette smoking, which should be OSHA's first objective. It is inaccurate to say that increases in cancer related to certain carcinogens are 'not yet observable' since the latency period is related to the dosage to which one is exposed. Finally, the statement that benign tumors are equally as important as malignant tumors is erroneous and unacceptable. (12 refs)

- 79-4808 The Carcinogenicity of Vinyl Chloride. (Eng) Gričute, L. (Unit Environmental Carcinogens, International Agency Res. Cancer, Lyon, France). *IARC Sci Publ* (22): 3-11; 1978.

Data on the carcinogenicity of vinyl chloride (VC) are summarized. Chronic exposure of laboratory animals to VC produces hepatic lesions and bone changes similar to those described in humans. In the first animal study implicating VC as a carcinogen, rats were exposed to 30,000 ppm VC, 4 hr/day, 5 days/wk, for 9-12 mo. They developed auditory sebaceous gland tumors and osteochondromas. Inhalation exposure in rats, mice, hamsters, and rabbits produced angiosarcomas of the liver and other organs and malignant tumors of the lung, intestine, kidney, skin, mammary gland, and forestomach. VC is carcinogenic in rats at 25 and 50 ppm in air and in mice and hamsters at 50 ppm in air. Ingestion of VC by gavage (50.0 and 16.6 mg/kg/day for 52 wk) produced liver angiosarcomas and other tumors in rats, but 3.3 mg/kg/day produced angiosarcomas at sites other than the liver. Transplacental administration of VC to rats between days 12 and 18 of gestation produced angiosarcomas. The in vitro mutagenicity of VC to bacteria is greatly enhanced by liver tissue homogenates from humans, mice, and rats. Chloroethylene oxide is considered to be the main active carcinogenic metabolite of VC; it is a strong alkylating agent that is responsible for mutagenesis in bacteria, yeast, and Chinese hamster cells. VC produces chromosome alterations in human lymphocytes. Primary liver angiosarcoma is the tumor observed in workers in the polyvinyl chloride (PVC) industry. This tumor is extremely rare in the general population, and those detected in PVC workers represent a 400-fold increase over the expected incidence. It is not known whether VC induces other tumors in humans. The av latent period

between initial VC exposure and liver angiosarcoma diagnosis is 20 yr. (34 refs)

- 79-4809 Ethylene Oxide: Toxicology Review and Field Study Results of Hospital Use. (Eng) Glaser, Z. R. (Div. Criteria Documentation and Standards Development, Natl. Inst. Occupational Safety and Health, Rockville, MD 20857). *J Environ Pathol Toxicol* 2(5, Special): 173-207; 1979.

Ethylene oxide (ETO) is used extensively within health care facilities to sterilize equipment and supplies. Recent results of mutagenesis tests have increased the concern for potential health hazards associated with exposure to ETO. Data from a National Institute for Occupational Safety and Health (NIOSH) report, in which evidence for the toxic effects of ETO, especially its mutagenic, teratogenic, and carcinogenic potentials, was assessed, are presented. Additionally, a limited field survey was conducted by NIOSH to document the use, problems, and potential for human exposure in medical facilities. Based on this review, measures for the control of occupational exposure have been recommended. The report includes a summary of the airborne ETO concentrations measured within health care facilities. NIOSH estimates that there are >10,000 ETO sterilizers in use in US health care facilities and that approx 75,000 workers are potentially exposed to ETO in these facilities. Reasons for the unnecessary exposure of personnel were found to include improper or inadequate ventilation of sterilizers, aerators, and working spaces; improper handling and/or storage of sterilized items; untrained workers operating some sterilization equipment; improper operating techniques leading to mishandling of some ETO sterilizing equipment; poor design of the sterilization facility; and design limitations of the sterilization equipment. (130 refs)

- 79-4810 Asbestos-enhanced Uptake of Carcinogens (2 Letters to Editor). (Eng) Light, W. G. (Technology Development Dept., Walden Div., Abcor, Inc., 850 Main St., Wilmington, MA 01887); Lakowicz, J. R.; Hylden, J. L.; Bevan, D. R. *Nature* 279(5711): 349-350; 1979.

The previously reported increased rate of transfer of benzo(a)pyrene (BP) adsorbed to particulate silica or amosite asbestos, compared with BP in a microcrystalline form, is suggested to result principally from adsorption of mobile dipalmitoyl L- α -phosphatidylcholine vesicles onto the particulate surface, rather than from increased solubilization of BP in an aqueous state. The preferential interfacial transfer of carcinogens to cell membranes and/or lung surfactant at the particulate surface may be an important factor in cocarcinogenesis. The first authors defend their conclusion concerning increased solubilization of BP by virtue of its association with particulate materials. (5 refs)

- 79-4811 Environmental Intoxicants and Their Fundamental Interactions. (Eng) Eisinger, J. (Bell Labs., Murray Hill, NJ 07974); Blumberg, W. E. *Q Rev Biophys* 11(4): 429-437; 1978.

Diseases of environmental origin and their role in an industrial society are reviewed. The manifestations of adverse environments can be divided into two groups: (1) widely distributed environmental conditions (ie, asbestos, aflatoxin, zeolite, and polycyclic aromatic hydrocarbons and (2) environmental health disasters that result from heavy exposure of a localized population to a toxic environment (ie, lead, methyl mercury, and chlorinated dibenzo-p-dioxins). The first group is generally associated with a low incidence of disease. The related health problems are difficult to trace and often are not recognized. (24 refs)

- 79-4812 Community Air Pollution in Canada: A Review and Predictions for the 1980's. (Eng) Bates, D. V. (Dept. Health Care and Epidemiology, Univ. British Columbia, 2075 Wesbrook Mall, Vancouver, British Columbia, V69 1W5, Canada). *Can Med Assoc J* 120(10): 1252-1256; 1979.

Changes in the most commonly measured air pollutants in Canada since nationwide air sampling began in 1971 are reviewed. The major pollutants include sulfur dioxide, suspended particulates, and nitrogen dioxide and ozone. Other pollutants considered are arsenic, which has been linked to lung cancer, and asbestos, which has been linked to pleural mesothelioma. There is increasing worry about community air pollution in cities with large metal-fabricating plants, and community exposure to asbestos fibers is likely to be of concern in the 1980's. (17 refs)

- 79-4813 Chemically Induced Occupational Cancer. (Ger) Heese, B. (Bayerische Akademie für Arbeits- und Sozialmedizin, Pfarrstrasse 3, 8000 Munich 22, W. Germany). *Munch Med Wochenschr* 97(18): 837-838,855; 1979.

Data on industrial chemical carcinogens are reviewed briefly. Arsenic, soot, tar, asbestos, aromatic amines, radiation, benzene, nickel, chromium-containing dust, dichlorodimethyl ether, chlorodimethyl ether, and vinyl chloride are the major industrial carcinogens. (no refs)

- 79-4814 The Carcinogenicity of Lead. (Eng) Moore, M. R. (Dept. Medicine, Gardiner Inst. Medicine, Western Infirmary, Univ. Glasgow, Glasgow G11 6NT, Scotland); Meredith, P. A. *Arch Toxicol* 42(2): 87-94; 1979.

A review of the carcinogenic potential of lead in man is presented. Lead is known to have specific effects on the cytochrome P450 system in animals and man and thereby to depress the mixed function oxidase system; thus lead may conceivably influence the potential carcinogenicity of many compounds. Animal studies have provided evidence of the carcinogenicity of lead by itself. Studies in rats with lead phosphate and lead acetate are described. Many of the studies have led to inconclusive results. The possible mechanisms for the carcinogenic effect of lead compounds are discussed briefly. Human studies have relied on geographic associations and industrial studies. The variations in cancer mortality rates in different areas in the world have been investigated; however, there are so many variables to consider that it is difficult to select those which are truly correlated with cancer. Various industrial studies of workers exposed to various lead compounds have provided no evidence to suggest that exposure to lead salts causes cancer of any site in man. Since the kidney is responsible for lead excretion during periods of excessive exposure, it was thought that an increase in kidney tumors would be observed; however, no such association was seen. The animal studies indicate considerable species and sex differences in the carcinogenicity of lead, and human studies have not proven that lead causes cancer in man. (71 refs)

- 79-4815 Environmental Causes of Cancer in Childhood. (Eng) Miller, R. W. (Epidemiology Branch, NCI, Bethesda, MD 20014). *Adv Pediatr* 25: 97-119; 1978.

Several environmental agents that cause cancer have short enough latent periods so that exposure and the diagnosis of neoplasia occur within the pediatric age-span. In other instances, the neoplasm occurs during adulthood but originates from prenatal or childhood exposures. Exposure to ionizing radiation has been linked with childhood acute leukemias and chronic myelogenous leukemia, thyroid tumors, and breast cancer. Ionizing radiation poses some cancer risk no matter how small the dose. Asbestos exposure during childhood (1) induces mesothelioma in adulthood and (2) may potentiate the capacity of cigarette smoking later in life to induce lung cancer. Potential transplacental carcinogens include alkylating agents, benzene, immunosuppressants, phenacetin, diethylstilbestrol, and diphenylhydantoin. The possibility of a leukemogenic effect should be considered when cytotoxic agents are used to treat children likely to be long-term survivors of their malignant or nonmalignant disease. Other chemical agents include anabolic androgenic steroids, immunosuppressants, polyvinyl chloride, and dietary contaminants. With respect to viruses and leukemia, a variety of hypotheses has been tested concerning the vertical or horizontal transmission of leukemia, especially in children, but none has been proved. Viruses have been associated with Hodgkin's disease, Burkitt's

lymphoma, nasopharyngeal carcinoma, and carcinoma of the uterine cervix. Concepts about the viral etiology of cancer have had to be adapted to fit observations in children concerning candidate viruses. Genetic influences and their interactions with radiation, viruses, and chemicals are also reviewed. (130 refs)

- 79-4816 The Mutagenicity of Trimethylphosphate. (Eng) Connor, T. H. (Univ. Texas Medical Branch, Galveston, TX). *Mutat Res* 65(2): 121-131; 1979.

The mutagenicity of trimethylphosphate (TMP), a fuel additive, industrial chemical, and flame retardant, is reviewed. TMP can produce a variety of genetic damage in many diverse systems. However, this damage is usually only manifested at relatively high doses. The overall acute and chronic toxicity of TMP is low. In a National Cancer Institute carcinogenicity study, rats received up to 300 mg/kg/wk and mice received up to 1,500 mg/kg/wk by gavage for 2 yr. TMP induced adenocarcinomas of the uterus/endometrium in the female mice (18%-38% incidence) and benign fibromas of the sc tissue in the male rats. There was no evidence of an increased tumor incidence in other tissues or organs in these animals. At high doses, TMP produces temporary sterility in mice, rats, rabbits, and *Drosophila* and dominant lethal effects in several mouse strains. The latter included increases in early fetal deaths and preimplantation losses that coincided with the postmeiotic stages of spermatogenesis. TMP produces a weak mutagenic effect in different microbial systems. It is concluded that TMP is a relatively weak mutagen in most systems although it produces a wide range of genetic damage, most probably due to its methylating capacity. (33 refs)

- 79-4817 Cyclophosphamide in Chronic Active Hepatitis (Letter to Editor). (Eng) Althouse, R. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, Lyon, France); Huff, J. E.; Tomatis, L.; Wilbourn, J. D. *Br Med J* 1(6178): 1630-1631; 1979.

There are at least 64 case reports of cancer (mostly leukemias, lymphomas, and bladder cancers) in patients treated with cyclophosphamide for a variety of malignant and nonmalignant diseases. This drug also causes cancer in mice and rats when administered in doses similar to those used in clinical practice. The few epidemiological studies suggest that over a period of 10 yr, between 5% and 15% of patients treated with alkylating agents will develop cancer. (8 refs)

- 79-4818 Drug Safety: Phenacetin (Letter to Editor). (Eng) Macklin, A. W. (Wellcome Res. Labs.,

3030 Cornwallis Road, Research Triangle Park, NC 27709); Welch, R. M.; Cuatrecasas, P. *Science* 205(4402): 144-148; 1979.

Previous assertions supporting the view that phenacetin (PA) is a carcinogen are criticized. Numerous negative feeding studies of PA are cited: a 2-yr study in Sprague-Dawley rats (20-200 mg/kg/day), a 31-mo study in Berlin-Druckery rats (>100 mg/kg/day), an 18-mo study in C57BL/6 mice (up to 754 mg/kg/day), studies in Fischer 344 rats and B6C3F1 mice (500 mg/kg/day), and two studies in dogs (20-450 mg/kg/day for up to 30 mo). The methodology of the previously cited positive animal studies is criticized. The processing of the pelleted diets involved temperatures beyond the melting point of PA. At these high temperatures, reactive N-oxidation products can be formed, and chemical reactions between dietary components and degradation products of PA might occur. One diet contained fish meal, a product that contains N-nitroso compounds and relatively large amounts of secondary amines and is often preserved with nitrites. Other reactions between degradation products of PA might occur in the acidic environment of the upper gastrointestinal tract. Po treatment of animals with N-hydroxyphenacetin, a urinary metabolite of PA that is unstable and is able to form azo and nitroso compounds under the acid or alkaline conditions of the gastrointestinal tract, is not a valid assay. PA has not been demonstrated to be mutagenic with or without metabolic activation, and it does not efficiently nitrosate under physiological conditions. (28 refs)

79-4819 Hazardous Nitrite (Letter to Editor)? (Eng) Clelland, R. C. (Dept. Statistics, Wharton Sch., Univ. Pennsylvania, Philadelphia, PA); Bowers, E. J. *Chem Eng News* 57(28): 4; 1979.

The contention that the use of low levels of nitrite for preserving cured meats is a carcinogenic hazard is criticized. Although numerous references to linear extrapolations from extremely high dosage levels can be found in the literature, citations showing that feeding realistic diets containing properly cooked bacon and other meat products, cured with 40-120 ppm sodium nitrite, to experimental animals has resulted in detrimental health effects are lacking. In addition, nitrite and nitrate are synthesized in the human intestine and are routinely present in amounts >140 ppm. Nitrite is also a normal constituent of green vegetables and human saliva. (no refs)

79-4820 The Organic Chemistry of N-Nitrosamines: A Brief Review. (Eng) Anselme, J. P. (Dept. Chemistry, Univ. Massachusetts at Boston, Harbor Campus, Boston, MA 02125). *ACS Symp Ser* (101): 1-12; 1979.

The structure, synthesis, and reactions of N-nitrosamines,

particularly the N,N-dialkyl- and N,N-aryl-nitrosamines, are reviewed. (59 refs)

79-4821 Stereochemical Effects on N-Nitrosamine Chemistry. (Eng) Lyle, R. E. (Chemistry Dept., North Texas State Univ., Denton, TX 76203); Fribush, H. M.; Singh, S.; Saavedra, J. E.; Lyle, G. G.; Barton, R.; Yoder, S.; Jacobson, M. K. *ACS Symp Ser* (101): 39-56; 1979.

The electronic arrangement of the nitrosamine function provides an interesting stereochemical consequence which may be as significant in the biochemistry of nitrosamine metabolism as in their chemistry. This review of stereochemical effects on N-nitrosamine metabolism includes conclusions concerning the electronic interaction and the electronic structure of the nitrosamine that can be drawn from its physical properties. (29 refs)

79-4822 Oxidative Activation of N-Nitrosamines: Model Compounds. (Eng) Michejda, C. J. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Kroeger-Koepeke, M. B.; Koepeke, S. R.; Kupper, R. J. *ACS Symp Ser* (101): 77-84; 1979.

Studies designed to contribute to an understanding of how nitrosamines are activated to produce the reactive electrophilic intermediates that interact with cellular components to elicit a carcinogenic response are reviewed. (26 refs)

79-4823 N-Nitrosamine Fragmentation and N-Nitrosamine Transformation. (Eng) Loeppky, R. N. (Dept. Chemistry, Univ. Missouri-Columbia, Columbia, MO 65211); Gnewuch, C. T.; Hazlitt, L. G.; McKinley, W. A. *ACS Symp Ser* (101): 109-123; 1979.

The fragmentation and transformation reactions of N-nitrosamines are reviewed. The nitrosation of 1-substituted aziridines illustrates that tertiary amine nitrosation can occur by elimination or substitution on the nitrosaminium intermediate. When a product of this reaction, nitrosaminoacetate, is treated with 50% aqueous ethanol, a cleavage reaction occurs, yielding benzylbutylnitrosamine and benzaldehyde. This cleavage reaction is a general property of β -hydroxynitrosamines, (β -HNA's), and a preliminary review of work in this area is given. Impetus for this work was provided by the fact that several β -HNA's are prevalent environmental contaminants and by the possibility that this type of cleavage reaction could potentiate or diminish the carcinogenicity of these nitrosamines. The base-catalyzed cleavage of β -HNA's

produces a smaller fragment nitrosamine and a carbonyl compound. The nitrosamine products obtained by treating β -HNA's with potassium tert-butoxide in tetrahydrofuran are tabulated. The rates of cleavage for a number of different β -HNA's are given. The mechanism of the base catalysis in this transformation reaction is currently under investigation and is not completely understood. Several significant side transformations of the reaction are illustrated. The possible relevance of base-catalyzed transformations of nitrosamines to nitrosamine carcinogenesis is reviewed, with emphasis on the fact that there have been few reports of chemical alterations that change the carbon skeleton of the nitrosamine. (23 refs)

- 79-4824 Carcinogenic Nitroso Compounds in Food Products. (Rus) Arkhipov, G. N. (Inst. Nutrition, Moscow, USSR); Zhukova, G. F.; Pimenova, V. V. *Vopr Pitan* (2): 12-21; 1979.

Literature pertaining to the level of carcinogenic nitroso compounds in food products is reviewed. Analysis of foods by chromatography, fluorometry, spectrophotometry, and mass spectrometry showed that the highest levels of nitroso compounds are found in processed meat and fish (up to 207 $\mu\text{g/kg}$). (95 refs)

- 79-4825 Laboratory Animal Feed (Letter to Editor). (Eng) Knapka, J. J. (Veterinary Resources Branch, Div. Res. Services, NIH, Bethesda, MD 20205). *Science* 204(4400): 1367; 1979.

A previous study in which a high nitrosamine (NA) concentration (52 ppb) was found in a sample of National Institutes of Health (NIH) laboratory animal feed may have tested the effects of manufacturing procedures on NA stability rather than NA concentrations in specific diets. This sample was also the only complete diet tested that was not subjected to a manufacturing process involving heat treatment. In addition, only a single bag was sampled. More recent studies of samples taken from different batches of the NIH diet have revealed NA concentrations ranging between 1.1 and 6.4 ppb. The fish meal used in the diet formulation contained up to 172 ppb volatile NA's. (7 refs)

- 79-4826 α -Amino Nitrite Esters and Their Analogues: Possible Reactive Intermediates in N-Nitrosamine Formation? (Eng) Keefer, L. K. (Analytical Chemistry Section, Lab. Carcinogen Metabolism, NCI, Bethesda, MD 20014). *ACS Symp Ser* (101): 91-108; 1979.

It is postulated that α -dialkylamino nitrite esters are involved as intermediates in a number of nitrosamine-forming

reactions of interest in environmental carcinogenesis. These species are proposed to fragment to nitrosamines and carbonyl compounds by way of intramolecular interaction between the nucleophilic amino function and the electropositive nitrosyl nitrogen atom. The fact that a variety of seemingly diverse transformations can be mechanistically unified by invoking this pathway is taken as evidence that α -dialkyl nitrosamines do in fact have at least transitory existence. (29 refs)

- 79-4827 Nitrosamines from Pesticides. (Eng) Oliver, J. E. (Beltsville Agricultural Res. Center, Beltsville, MD 20705). *Chemtech* 9(6): 366-371; 1979.

Certain nitrogen-containing pesticides, as residues in soil, water, plants, etc, may be nitrosated by indigenous nitrite or by other nitrosating agents--eg, nitrogen oxides from automobile exhausts or other fuel consumption. In addition, pesticides may contain nitroso compounds as impurities. (48 refs)

- 79-4828 N-Nitrosamines: Their Occurrence and Prevention. (Dut) Stephany, R. W. (Afdeling voor Biologisch-Residu Onderzoek, Rijksinstituut voor de Volksgezondheid, Bilthoven, Netherlands); Schuller, P. L. *Chem Weekbl*: 373-376; 1979.

Studies of N-nitrosamines (NA's) and their occurrence are reviewed. About 100/130 NA's investigated for their biological effects were found to be carcinogenic. These compounds are characterized by strong organotropicity. Symmetric dialkyl-NA's, administered po, induce liver cancer, but asymmetrical methylalkyl-NA's usually induce cancer of the esophagus. Some carcinogenic NA's also occur in food; they include N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosopyrrolidine, and N-nitrosopiperidine. Dialkyl-NA's such as N-nitrosodimethylamine are found in meat and meat products, seafood, cheese, distilled beverages, wine, and beer. Cyclic NA's such as N-nitrosopyrrolidine are found in meat, seafood, and beer. Dialkyl-NA's and N-nitrosornicotine are found in tobacco smoke. (10 refs)

- 79-4829 Chromosomal Effects of Mutagenic Carcinogens and the Nature of the Lesions Leading to Sister Chromatid Exchange. (Eng) Wolff, S. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143). In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 208-215; 1978.

Studies of the induction of sister chromatid exchanges

(SCE's) in Chinese hamster ovary (CHO) cells and xeroderma pigmentosum (XP) cells are reviewed. In CHO cells, UV rays and chemical mutagens such as acetox-yacetylaminofluorene and 4-nitroquinoline 1-oxide induce long-lived DNA lesions, which lead to SCE formation when the cells pass through S. When SCE's are formed, both strands of the DNA double helix exchange with those in the sister chromatid. After UV treatment, the long-lived lesions do not seem to be thymine dimers since the production of SCE's is independent of excision repair, as measured by unscheduled synthesis or repair replication. Treatment of repair-defective XP cells with alkylating agents has indicated that the lesions responsible for SCE formation might be a minor unexcisable fraction of the damage. One possible candidate for this would be alkylation at the O⁶ position of guanine, which is ordinarily a minor alkylation product. (34 refs)

- 79-4830 Smoking and Health: A Report of the Surgeon General. (Eng) U. S. Department of Health, Education, and Welfare (Office Assistant Secretary Health, Public Health Service, U.S. Dept. Health, Education, and Welfare, Washington, DC). (Washington: Dept. Health, Education, and Welfare): 1164 pp.; 1979.

This new surgeon General's Report on Smoking and Health is a compendium of new data confirming the conclusions of the original report published in 1964 and it reveals, with dramatic clarity, that cigarette smoking is even more dangerous than was supposed in 1964. It presents sobering information about women and smoking. Evidence suggests that mothers who smoke during pregnancy may create long-term, irreversible effects on their babies. The female mortality rate from lung cancer was three times higher in 1978 than in 1964, and women who have smoking characteristics similar to those of men experience similar overall mortality rates. Health risks to smokers exposed to certain occupational hazards are dramatically increased, and they include workers in the asbestos, rubber, coal, textile, uranium, and chemical industries. New evidence has accumulated with respect to relationships between tobacco use and cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas. Cigarette smoking is causally related to lung cancer in men and women, and the risk of developing lung cancer increases with increasing dosages of smoking, as measured by number of cigarettes smoked per day, duration of smoking, age of initiation of smoking, degree of inhalation, tar and nicotine content of cigarettes smoked, and several other measurements. Prospective studies have shown that mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus are approx equal in users of cigars, pipes, and cigarettes. Although several factors appear to be involved in lip cancer development, pipe smoking alone or in combination with other forms of smoking is causally related to this cancer. Pipe and cigar tobacco condensates have a carcinogenic potential comparable to that of cigarette condensates. (3303 refs)

- 79-4831 α , β Mannitone, a New Industrial Material with Unknown Benefits and Risks. (Eng) Schneiderman, M. A. (Field Studies and Statistics Program, NCI, Bethesda, MD 20014). *IARC Sci Publ* (25): 237-239; 1979.

α , β -mannitone, a substance made from old automobile tires, has not been completely characterized, and its risks and benefits are discussed. The substance has been proposed for use as a gasoline substitute. (no refs)

- 79-4832 The Genotoxic Effects of 2,4,5-T. (Eng) Grant, W. F. (Genetics Lab., McGill Univ., Macdonald Campus, Ste. Anne de Bellevue, Quebec H9X 1CO, Canada). *Mutat Res* 65(2): 83-119; 1979.

The cytogenetic, carcinogenic, and teratogenic properties of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) are reviewed. Commercial formulations contain up to 0.1 ppm of the contaminant dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD), which causes birth defects and tumors in animals at levels <100 parts per thousand. 2,4,5-T is a clastogen that produces chromosome aberrations, including bridges and micronuclei, in a variety of animal and plant species. In addition, 2,4,5-T induces cell enlargement, lengthens the duration of the mitotic cycle, extends DNA synthesis, induces mitosis, and causes chromosome contraction, stickiness, and sticky bridges, all at low concentrations. C mitoses, multinucleate cells, polyploidy, reduced fertility, and species resistance have also been reported. In vivo production of chromosome aberrations in humans is inconclusive. The emulsifiers and solvents in commercial preparations of 2,4,5-T also induce chromosome aberrations. In >20 experiments involving 15 different systems, only 3 reported 2,4,5-T to be mutagenic: 2/4 sex-linked lethal tests in *Drosophila* and 1/2 studies with *Saccharomyces cerevisiae*. In one study in which 2,4,5-T was given to mice in daily doses of 21.5 mg/kg in the diet, the herbicide did not increase the number of tumors significantly. In another study, administration of 12 mg/kg/day in the diet significantly increased the incidence of neoplastic lesions in C3Hf mice. Although the data on teratogenicity are not clear-cut, several reports suggest that 2,4,5-T is teratogenic with and without TCDD and that 2,4,5-T and TCDD may potentiate teratogenicity. (131 refs)

- 79-4833 The Development of Various Formulations of Vulcanizing Accelerators. (Ger) Rijnders, R. F. (Akzo Chemie BV, Amersfoort, Netherlands); Katzanevas, A. *Gumm Asbest Kunststoffe* 32(5): 309, 312-316; 1979.

The hygienic, toxicological, technological, and economical aspects of vulcanizing accelerators in rubber production

are reviewed. Experiments on laboratory animals demonstrated the carcinogenic and teratogenic effects of certain vulcanizing accelerators (not specified). These findings prompted rubber manufacturers to undertake retrospective studies into the causes of death among their workers. The results obtained so far have not confirmed the teratogenic and bladder cancer-inducing effects of ethylene thiourea, a substance thought to be carcinogenic and teratogenic. (31 refs)

- 79-4834 Drug-Induced Second Diseases in Patients with Rheumatism. Possibilities of Prevention and Therapy. (Ger) Chlud, K. (II. Medizinische Abteilung, Kaiser-Franz-Joseph-Spital der Stadt Wien, Kundratstrasse 3, A-1100 Vienna, Austria). *Therapiewoche* 29(23): 3981-4004; 1979.

D-Penicillamine treatment causes reversible bone marrow aplasia and lupus erythematosus in some patients with rheumatism. A significantly increased incidence of neoplasms and systemic diseases was observed in rheumatic patients following long-term therapy with cytostatics, eg, triaziquone. (56 refs)

- 79-4835 Mutagenic Agents: Methods of Detection and Clinical-Pathological Correlations. (Ita) Migone, N. (Cattedra di Genetica medica, Universita, Parma, Italy); Savi, M. *Recent Prog Med* 65(4): 340-365; 1978.

The general problems of mutagenesis, mutagenic agents, and test systems for their detection are reviewed. Close correlations were found between the mutagenic and carcinogenic activities of various substances (aromatic amines, alkylating agents, polycyclic aromatic hydrocarbons, esters, epoxides, carbamates, nitroaromatic and heterocyclic compounds, nitrosamines, toxins, antibiotics, cigarette smoke condensate, azo dyes, and diazo compounds). Some potent mutagens (triaziquone, triethylenephosphoramide, triethylene melamine, butylnitrosocarbamide, and methylmethane sulfonate), and weak mutagens (tripaflavine, 3,4-benzopyrene, and aflatoxin) were found to have mutagenic activity both in mammals and in microorganisms without metabolic activation, while hydrazine and captan (potent mutagens), as well as caffeine, dichlorvos, formaldehyde, and urethane (weak mutagens), were found to be mutagenic in microorganisms but not in mammals. Cyclophosphamide, nitrosomorpholine, dimethylnitrosamine, and dinitrosopiperazine were found to be non-mutagenic in microorganisms and mammals alike. (87 refs)

- 79-4836 Current Status of Experimental Chemical Carcinogenesis and Its Applications to Human

Cancer Risk. (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701). *Cancer Res* 39(7, part 2): 2887-2890; 1979.

Experimental chemical carcinogenesis and its application to human cancer risks are reviewed. Polynuclear hydrocarbons comprise the most extensively studied group of carcinogens. Their chemical structure specificity compatible with carcinogenicity is quite marked. The most notable feature of these carcinogens is their restricted carcinogenic action. At low doses, they can also act as initiating agents. A recent study indicated that phenobarbital acts as a promoting agent in the liver of rats treated with low doses of carcinogens. Ethanol may act by a similar mechanism as a tumor promoter for human liver. It is reasonable to assume that the cancers seen in humans are the result of the compounding of a large number of relatively small exposures to compounds that increase cancer risk. All main classes of carcinogens except the N-nitroso compounds show a strong species specificity. No species has been found to be resistant to nitrosamines, and it may be significant that many N-nitroso compounds are found in the environment. The most notable characteristic of these compounds is their pronounced organ specificity. Problems related to extrapolation from experimental animal carcinogenesis are also discussed. Such studies provide information on the patterns and mechanisms of action of carcinogens. (13 refs)

- 79-4837 Organics. (Eng) Chian, E. S. (Sch. Civil Engineering, Georgia Inst. Technology, Atlanta, GA); DeWalle, F. B.; Meng, H.; Norman, D. *J Water Pollut Control Fed* 51(6): 1134-1171; 1979.

The results of studies on the detection, identification, and quantification of a number of organic compounds are summarized and tabulated together with the methods used in these studies. Compounds considered include detergents and surfactants; aliphatic and aromatic hydrocarbons; pesticides, chlorinated hydrocarbons, and related compounds; humic acids and naturally occurring organics; and organics present in water. (327 refs)

- 79-4838 Cell Regulation and Cancer. (Eng) Weinstein, I. B. (Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032). *Differentiation* 13(1): 65-66; 1979.

The characteristics of tumor-initiating and -promoting agents are presented, and the molecular nature of active derivatives of the tumor initiator benzo(a)pyrene is reviewed. In addition, the cellular effects of the most efficient tumor promoter, 12-O-tetradecanoylphorbol-13-acetate, are described. (11 refs)

REVIEW

- 79-4839 Aryl Hydrocarbon (Benzo(a)pyrene) Hydroxylase Induction in Cells in Culture. (Eng) Whitlock, J. P. (Dept., Pharmacology, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Gelboin, H. V. *Pharmacol Ther [A]* 4(3): 587-599; 1979.

The aryl hydrocarbon hydroxylase (AHH) enzyme system is inducible in cultured cells by a wide variety of polycyclic hydrocarbons. The inducible cells include secondary cultures, cell lines, cell hybrids, and lymphocytes and monocytes. In general, the enzyme level rises after a 30-60 min lag period following the addition of inducer. The increase in AHH levels can reach thirtyfold or greater at 16 hr. The induction process is sensitive to actinomycin D and is, therefore, dependent on RNA synthesis. This dependence occurs only during the first few hours of the induction process. The induction process requires RNA synthesis initially, followed by protein synthesis, and these steps can be experimentally dissociated. The induction-specific RNA is not ribosomal RNA and is probably poly A-containing heterogeneous nuclear RNA. Induction can be accomplished by the addition of a polycyclic aromatic hydrocarbon inducer, by temporary inhibition of protein synthesis, or by cyclic AMP. These induction processes are synergistic, suggesting that there are at least three mechanisms of AHH induction. The gene action system responsible for AHH induction interacts in some manner with the steroid system regulating tyrosine aminotransferase, since synergistic effects between the steroid and polycyclic hydrocarbons are observed. Studies with cloned cells indicated that a nongenetic regulatory mechanism may influence basal and inducible AHH levels; studies with human-mouse hybrids indicate that AHH expression is associated with human chromosome 2. Studies of AHH induction in lymphocytes and monocytes of fraternal and identical twins suggest strong genetic determinants in AHH levels in humans. (47 refs)

- 79-4840 The *Ah* Locus: Genetic Regulation of the Metabolism of Carcinogens, Drugs, and Other Environmental Chemicals by Cytochrome P-450-mediated Monooxygenases. (Eng) Nebert, D. W. (Nat. Inst. Child Health and Human Development, NIH, Bethesda, MD); Jensen, N. M. *CRC Crit Rev Biochem* 6(4): 401-437; 1979.

The role of the *Ah* locus in genetic regulation of the metabolism of carcinogens and other compounds by cytochrome P-450-mediated monooxygenases (MO's) is reviewed. The *Ah* locus controls the induction of at least 20 MO activities and associated cytochrome(s) P₁-450 by 3-methylcholanthrene (3-MC) and other polycyclic aromatic compounds. N-Acetylarlyamine N-hydroxylase induction and the induction of some of the other 20 MO activities may be associated with other cytochromes. Other induced macromolecules that appear to be under the same regulatory control include microsomal uridine diphosphate glucuronosyltransferase, cytosolic reduced NAD(P):mena-

dione oxidoreductase, and cytosolic ornithine decarboxylase. One product of the regulatory *Ah* gene is believed to be a cytosolic receptor protein that has a high affinity for polycyclic aromatic inducers and appears to have diminished affinity in mice that are unresponsive to aromatic hydrocarbons. Regulation of responsiveness probably involves several alleles at more than one locus, but differences between responsive C57BL/6 and nonresponsive DBA/2 mice can be almost completely explained by differences at the *Ah* locus. Compared with *Ah-d/Ah-d* mice, *Ah-b/Ah-b* and *Ah-b/Ah-d* mice show, among other things, a high susceptibility to 3-MC- and benzo(a)pyrene (BP)-induced sc sarcomas, 3-MC-induced lung tumors, and BP-induced leukemia. The *Ah-b* allele is associated with a high mutational rate in *Salmonella* by metabolic activation of several chemical carcinogens and increases in numerous specific metabolites of chemical carcinogens bound to DNA nucleosides. There is also evidence that heritable variations in aryl hydrocarbon hydroxylase inducibility occur in humans. (169 refs)

- 79-4841 The Role of Glutathione and Glutathione S-Transferases in the Metabolism of Chemical Carcinogens and Other Electrophilic Agents. (Eng) Chasseaud, L. F. (Dept. Metabolism and Pharmacokinetics, Huntingdon Res. Centre, Huntingdon, England). *Adv Cancer Res* 29: 175-274; 1979.

The role of glutathione (GSH) and GSH S-transferases in the metabolism of chemical carcinogens and other electrophilic agents is reviewed. The mode of action, assay and stability, intracellular location, tissue distribution, species distribution, maturation, induction, inhibition, and sex differences of the GSH S-transferases are covered. Metals and 22 different classes of compounds (including mutagens and carcinogens) that conjugate with GSH are treated individually. Conjugation with nucleophilic GSH is important for the elimination of electrophilic foreign compounds from the body, and conjugation is generally catalyzed by the GSH S-transferases. GSH conjugates are most likely excreted in the bile, but the subsequent fate of the biliary-excreted products has not been fully investigated. Clues as to whether or not GSH is involved in conjugation with a particular electrophile can be provided by studies of the depletion of hepatic and, sometimes, extrahepatic GSH that may occur when the electrophile or its precursors are administered to laboratory animals. None of the studies reviewed clearly showed that GSH and its associated S-transferases prevented a potential carcinogen from exerting its effects. There is, however, an apparent inverse correlation between the level of ligandin-binding activity in the liver cell, which is affected by certain drug or hormonal manipulations, and the susceptibility of the cell to chemically induced carcinogenesis. (698 refs)

- 79-4842 The Pharmacology of Graft Rejection. (Eng) Lewis, G. P. (Dept. Pharmacology, Royal

Coll. Surgeons England, London WC2A 3PN, England); Mangham, B. A. *Trends Pharmacol Sci* 1(Inaug. Issue): 18-21; 1979.

Graft rejection (GR) is a complicated process in which more than one mediator participates. Pharmacological studies of GR, which are reviewed here, have been aimed at identifying these mediators. Specific topics include the role of histamine and prostaglandins in GR, interaction of mediators with cyclic AMP and cyclic guanosine monophosphate, and the possible role of complement in GR. (18 refs)

- 79-4843 Enzymic Modification of Environmental Intoxicants: The Role of Cytochrome P-450. (Eng) Blumberg, W. E. (No affiliation given). *Q Rev Biophys* 11(4): 481-542; 1978.

The distribution of environmental intoxicants on the earth and the metabolism of these chemicals by in vivo detoxification systems are reviewed. Many intoxicants are detoxified by cytochrome P-450 enzyme systems, and others are potentiated by the same systems. The intoxicants that are potentiated by cytochrome P-450 are generally believed to be more dangerous than those that are detoxified by it. (57 refs)

- 79-4844 The Antioxidant Vitamins. (Eng) Johnson, F. C. (J.A. Pye Res. Centre, Haughley Res. Farms, Ltd., Haughley Stowmarket, England). *CRC Crit Rev Food Sci Nutr* 11(3): 217-309; 1979.

The chemistry and analysis of vitamin C and vitamin E are reviewed, as are their sources and fates during processing and cooking, their absorption and metabolic actions in vivo, and their participation in metabolic defense mechanisms. The increasing importance of work on free-radical reactions, their toxicity and carcinogenic action, and their relation to the metabolism of metals, particularly Fe, Cu, Se, and Zn, shows a number of metabolic pathways with which both vitamins interact. (505 refs)

- 79-4845 Bronchial Epithelium and Cigarette Smoking (5 Letters to Editor). (Eng) Kurt, T. L. (Southwestern Medical Sch., Dallas, TX 75205); Haack, D. G.; Miller, G. H.; Harada, W.; Pearson, L.; Schumaker, J. A.; Bernfeld, P.; Auerbach, O.; Hammond, E. C.; Garfinkel, L. *N Engl J Med* 300(24): 1394-1396; 1979.

A report that fewer precancerous changes occurred in the lungs of male smokers who died during 1970-1977 than in those who died during 1955-1960, presumably due to the lower consumption of tar and nicotine, is commented on.

It is necessary to assess lifelong exposure to tar and nicotine rather than to classify a person as a smoker or nonsmoker. The earlier set of bronchial epithelium sections showed serious denudation, which would probably bias the evaluation of histologic changes. The age distribution was different in the two groups. The newer cigarettes burn for much shorter periods, and thus the two groups cannot be compared accurately based on number of cigarettes smoked/day. The authors of the report respond to these comments. (19 refs)

- 79-4846 Urinary Bladder Cancer: Potentials of and Problems Associated with Early Intervention Strategies. (Eng) Bryan, G. T. (Div. Clinical Oncology, Dept. Human Oncology, Clinical Science Center, 600 Highland Ave., Madison, WI 53792). *Semin Oncol* 6(2): 161-165; 1979.

Early intervention strategies in bladder cancer (BC) are reviewed. Because a disease state can be divided pathogenetically into identifiable stages, attempts to alter the course of the disease by modifying one of these stages are attractive intervention strategies. To form a clinically detectable neoplasm (approx 1 cm³, 10⁹ cells), a neoplastic cell and its progeny must undergo about 30 cell divisions; only about 7 more divisions are required to form a lethal mass. Hence, prevention and intervention strategies must occur before a detectable tumor exists. Since the average age at diagnosis of BL is 68 yr in the US, it is imperative to identify prospectively those individuals at increased risk. Recognized risk factors include age, sex, occupation, and smoking habits; possible risk factors are prior pelvic irradiation and consumption of coffee or artificial sweeteners. One intervention strategy is to add an agent or agents to the environment of an individual to interfere with hypothetical bladder carcinogenic mechanisms. These additives have one of three modes of action: (1) interference with carcinogen-target interaction (eg, β -glucuronidase inhibition, free-radical scavenger agents), (2) alteration of the molecular balance between activation and detoxication toward detoxication (eg, detoxication enzyme induction, inhibition of activation enzymes, addition of cofactors to inhibit carcinogen or promoter formation), and (3) inhibition of the growth and development of initiated cells by retinoids, protease inhibitors, etc. The effectiveness of these methods to date, largely unspectacular, is summarized. (28 refs)

- 79-4847 Anabolic Steroids and Liver Tumors. (Ger) Scheuer, A. (Medizinische Klinik, Universität Marburg, Mannkopfstr. 1, 3550 Marburg, W. Germany); Gerdes, H.; Lehmann, F. G. *Dtsch Med Wochenschr* 104(21): 779-783; 1979.

Thirty-two cases of liver tumors following treatment with

anabolic steroids are reviewed and available data summarized. The drugs used were oxymetholone, methyltestosterone, methandienone, stanozolol, fluoxymesterone, oxandrolone, norethandrolone, nandrolone decanoate, testosterone propionate, testosterone enanthate, and testosterone cyclopentyl propionate. Eighteen patients received monotherapy, 13 sequential therapy. The duration of the treatment was 0-12 mo in 5 cases, 13-60 mo in 8, 61-120 mo in 12, and over 120 mo in 1. The total dose was 0-50 g in 6 cases, 51-100 g in 7, 101-150 g in 2, and over 150 g in 9. Five patients were aged 0-10 yr, 10 11-20 yr, 9 21-30 yr, and 8 were aged over 30 yr. The histological diagnosis was hepatocellular carcinoma in 14 cases, well-differentiated hepatoma in 9, hepatocellular adenoma in 8 (associated with the hepatocellular carcinoma in 1 case), and focal nodal hyperplasia in 2; peliosis hepatis was seen additionally in 11 cases. (58 refs)

- 79-4848 Cardiac Glycosides and Breast Cancer (Letter to Editor). (Eng) LeWinn, E. B. (8801 Stenton Ave., Philadelphia, PA 19118). *Lancet* 1(8127): 1196-1197; 1979.

Comments are made on the findings that patients on cardiac glycosides (digoxin) had breast cancers (BC) with a tumor cell population composed of cells that are smaller and more uniform in morphology, density, and size than those in patients not on digitalis (DT) and that after 2 yr of BC, distant spread was less common in patients on digitalis treatment. There have been several reports of a connection between the estrogen-like structure of DT and its ability to cause gynecomastia in men and in postmenopausal women. Cardiac glycosides might interfere with estrogen receptors, as suggested, but in some cases they also might have an exacerbating effect on BC. (5 refs)

- 79-4849 Is the Hypothesis on the Role of Rauwolfia Preparations in the Development of Breast Cancer Substantiated? (Rus) Tikhonova, H. A. (Cancer Res. Center, Moscow, USSR); Lazarev, N. I.; Samoilenko, L. A. *Klin Med (Mosk)* 57(5): 52-56; 1979.

Controversial data on the role of rauwolfia alkaloids, primarily reserpine, in the etiology of breast cancer are reviewed. In a number of experiments, reserpine was found to stimulate prolactin secretion, which causes cancer of the mammary gland in Sprague-Dawley rats. However, other data indicate that prolactin stimulates the function of mammary gland cells and not their division, and an elevated prolactin level can prevent or even inhibit the growth of mammary gland tumors. A retrospective analysis of the case histories of 494 women with primary breast cancer and 478 women with cancer at other sites (97 pulmonary carcinomas, 230 stomach carcinomas, 151 cervical carcinomas) showed that concomitant hypertension

was present in 118/494 and 91/478 patients, respectively. Of 118 patients with breast cancer and hypertension, 39 had received rauwolfia drugs, compared with 41/91 patients with other cancers and hypertension. The absence of a significant difference in the number of patients receiving rauwolfia drugs indicates that they do not have a carcinogenic effect. (19 refs)

- 79-4850 A Unifying Concept of Chorionic Gonadotrophin Production in Malignancy. (Eng) Skrabanek, P. (Dept. Endocrinology, Mater Misericordiae Hosp., Dublin, Ireland); Kirrane, J.; Powell, D. *Invest Cell Pathol* 2(2): 75-85; 1979.

The production of human chorionic gonadotropin (HCG) during malignancy is reviewed. HCG production by germ cell tumors is related to the presence of chorionic tissue or syncytial giant cells in which the presence of HCG can be demonstrated by immunocytochemistry. HCG-producing tumors other than gestational choriocarcinoma or germinomatous tumors are quite rare and are limited to the lung, liver, gastrointestinal tract, adrenal cortex, and urogenital tract. The histology and distribution of these "somatic" HCG-producing tumors are characteristic for the individual organs. The somatic and germ cell tumors associated with excess HCG production show marked similarity in clinical behavior, histology, and endocrine profile. This may indicate a common embryological origin or a common biochemical and genetic organization of certain malignant somatic and germ cells. Elevated HCG levels are also found in patients with various nonmalignant conditions. (127 refs)

- 79-4851 Indications, Modalities and Limits of Estrogen Therapy (Other than Contraception). (Fre) de Lignieres, B. (Service d'endocrinologie et de gynécologie medicale, Hopital Necker, 149, rue de Sevres, 75730 Paris Cedex 15, France); Mauvais-Jarvis, P. *Rev Prat* 29(21): 1723-1726, 1729-1732; 1979.

The physiological effects and long-term side effects of estrogen therapy in menopause are reviewed. The risk of cancer of the breast and endometrium is linked with the possible accumulation of estrogen in the target tissues and with the development of a zone of hyperplasia in the galactophores and endometrium. The risk of carcinogenesis can be prevented by the intermittent use of estrogens (during 3 wk/mo) and by the systematic administration of a synthetic progestogen for at least 10 days/mo. (11 refs)

- 79-4852 Oestrogen Therapy and Endometrial Cancer (Letter to Editor). (Eng) McDonald, A. D. (Dept. Epidemiology, St. Mary's Hosp. Medical Sch.,

London W2 1PG, England). *Lancet* 1(8129): 1288-1289; 1979.

Contrary to a previous editorial, an association between estrogen therapy (ET) and endometrial cancer (EC) has not yet been established. Since menopausal women on (ET) are subject to vaginal bleeding, silent EC's are likely to be detected and, since the distinction between hyperplasia and cancer is far from clear, some borderline cases may be classified as cancer. If EC patients are compared with nonbleeding controls (which was the case in 7 studies cited in the editorial), a spurious association with ET will be found. The editor agrees that presymptomatic EC may be more readily detected in women taking estrogens. Case selection should be restricted to women with invasive cancer, in whom there is little doubt about the diagnosis. Then, a positive association will still be evident. (12 refs)

- 79-4853 The Prostatic Carcinoma in Laboratory Animals. A Bibliographic Survey from 1900 to 1977. (Eng) Rivenson, A. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Dana Road, Valhalla, NY 10595); Silverman, J. *Invest Urol* 16(6): 468-472; 1979.

The spontaneous and artificially-induced occurrence of prostatic carcinoma in laboratory animals is reviewed. Contrary to the frequent occurrence of prostatic adenocarcinoma in man, laboratory animals have a low incidence of clinically manifest carcinoma of the prostate. The development of human prostatic cancers grafted into nude mice appears to be neither hormone nor sex-dependent. Almost all major carcinogens produce tumors of the prostate in laboratory animals. X-irradiation, steroid hormones, and various chemical carcinogens have been successfully employed, and malignant prostatic tissue has been obtained by inoculating normal hamster prostate with simian virus 40. A combination of hormones and carcinogens appears to be most satisfactory for the production of experimental animal models for human prostatic adenocarcinoma. (70 refs)

- 79-4854 Significance of the Working Environment for the Lungs. (Ger) Konetzke, G. (Abt. Berufs-krankheiten, Zentralinstitut für Arbeitsmedizin der DDR, Noldnerstrasse 42-44, DDR-1134 Berlin, E. Germany). *Z Gesamte Inn Med* 34(6): 57-59; 1979.

Occupational diseases of the lungs account for about 10% of all occupational diseases in E. Germany, averaging about 1,200 cases/yr. The incidence is highest for silicosis and asbestosis (about 300 cases/yr), which predispose to lung carcinoma and malignant mesothelioma. (13 refs)

- 79-4855 Endocrine Effects of Testicular Neoplasms. (Eng) Fox, H. (Dept. Pathology, Univ. Man-

chester, Manchester, England); Reeve, N. L. *Invest Cell Pathol* 2(2): 63-73; 1979.

Hormone abnormalities occurring in patients with testicular tumors are reviewed. Abnormalities of sex steroid secretion occur much more commonly than is generally realized. Gynecomastia in men with choriocarcinoma appears to result from an elevation of combinations of hormones with a physiological relationship to each other, and hormone disturbances in men with testicular seminomas or teratomas appears to be due to the presence of undetected choriocarcinomatous foci. Very few true sertoli cell tumors seem to be associated with signs of hormone disturbance. In one patient with a granulosa cell tumor, a low excretion of 17-oxosteroids and follicle-stimulating hormone and a marked elevation of urinary estrogens were demonstrated, abnormalities that lend support to the presumed estrogenic capacity of these rare neoplasms. Interstitial cell tumors appear to secrete estrogens and a variety of weak androgens. Some interstitial cell tumors have features typical of adrenocortical tissue. Gonadoblastomas also appear to be hormonally active, this activity being independent of their Leydig cell content. Other endocrine abnormalities associated with testicular tumors are quite rare. They include Cushing's syndrome, hypercalcemia, hyperthyroidism and the carcinoid syndrome. (94 refs)

- 79-4856 The Relevance of Photobiology. (Eng) Giese, A. C. (Dept. Biological Sciences, Stanford Univ., Stanford, CA 94305). *Bioscience* 29(6): 353-357; 1979.

In this survey of the contribution of photobiology to biology, attention is focused on research opportunities, especially those at the molecular level. If visible light is absorbed by critical molecules, it can be as effective as UV light in producing photobiological effects, such as activation of some enzymes, retardation of cell growth in culture, induction of chromosome aberrations and slowing of DNA synthesis in tissue culture cells, mutagenesis, and killing of repair-deficient bacteria. (24 refs)

- 79-4857 Plutonium and Other Heavy Radioactive Elements in Nature. (Ger) Keller, C. (Schule für Kerntechnik, Kernforschungszentrum Karlsruhe GmbH, Postfach 3640, D-7500 Karlsruhe 1, W. Germany); de Alleluia, I. B. *Chemiker-Zeitung* 103(4): 139-153; 1979.

The occurrence, origin, and general ecological significance of plutonium and other heavy radioactive elements in nature are reviewed. Due to very low uptake of plutonium by biological systems (resuspension and migration in soil and plants), the plutonium load of man is very low, averaging 5 p(pico)Ci/person in the U.S. The accumulation of

^{210}Po in tobacco plants represents a real hazard for smokers because it is volatile even below the combustion temperature of the cigarette (750 C) and is inhaled. The inhaled radioactivity is estimated at 0.1 pCi ^{210}Po /cigarette, which may represent an additional radiation load of up to 36 rem (roentgen-equivalent-man) after long-term heavy smoking. This radioactivity can also have a cocarcinogenic effect with the polycyclic aromatic hydrocarbons inhaled in cigarette smoke. Uranium, added to the ceramic material from which dental prosthesis is prepared (permissible level 0.05 wt % in the U.S.), can cause an annual radiation dose of up to 130 rem in the buccal mucosa. (91 refs)

- 79-4858 Comments on "Leukemia Risk from Neutrons" (Letter to Editor). (Eng) Beebe, G. W. (Clinical Epidemiology Branch, NCI-NIH, Landow Bldg., Rm. 5A21, Bethesda, MD 20014); Land, C. E. *Health Phys* 36(3): 465-466; 1979.

Questions concerning a previous study on leukemia risk from neutrons are raised. It was suggested previously that 1 rad delivered to the active bone marrow by fast neutrons may confer a lifetime risk of about 800 leukemias per million persons, and that a 50-yr occupational exposure at the maximum permissible dose of 5 roentgen-equivalents-man/yr may lead to a life-time induction of 2% for leukemia and 10% for all fatal cancers. (5 refs)

- 79-4859 RBE for Carcinogenesis by Fission Neutrons (2 Letters to Editor). (Eng) Mole, R. H. (Medical Res. Council, Radiobiology Unit, Harwell, Didcot., Oxon. OX11 0RD, England); Rossi, H. H.; Mays, C. W. *Health Phys* 36(3): 463-465; 1979.

A previous paper seems to assume that the relative biological effectiveness (RBE) for cancer induction by fission neutrons, as compared with γ -rays, is the same for all tissues. However, there is already good evidence that fission neutrons are not necessarily much more effective carcinogenic agents in humans than are γ -rays. The authors of the paper reply that the extension of their analysis of leukemia risk to other cancers was tentative and does not exclude the possibility that the RBE for certain cancers might be less or, perhaps, more. Organs (ie, breast and thyroid) in which there seems to be a lower RBE are subject to strong endocrine control, and the apparent difference in RBE may be due to a complex interaction of various cell systems. (12 refs)

- 79-4860 The Burn Patient: II. Later Care and Complications of Thermal Injury. (Eng) Pruitt, B. A. (No affiliation given). *Curr Probl Surg* 16(5): 1-95; 1979.

The use of primary grafting for closure of full-thickness burns has reduced the occurrence of burn scar carcinoma. The av latent periods of scar tissue carcinoma in two series were 34 and 36 yr. Keratoacanthomas may represent an intermediate stage of disordered healing between that characteristic of hypertrophic scar and scar carcinoma. Chronic trauma and repetitive reepithelization of poorly vascularized burn scars are important in the etiology of scar malignancies, which are usually of squamous cell histology. (228 refs)

- 79-4861 Photochemotherapy and Risk of Skin Cancer (Letter to Editor). (Eng) Pembroke, A. C. (Dept. Dermatology, King's Coll. Hosp., London SE5 9RS, England); Hehir, M. E.; du Vivier, A. W.; Marten, R. H. *Lancet* 1(8129): 1299; 1979.

A prospective study of the risk of cutaneous carcinoma in psoriatic patients treated with po methoxsalen photochemotherapy (PCT) is discussed. The study indicated that patients treated with PCT were more prone to cutaneous carcinoma. However, this phenomenon could have been a result of previous treatment, such as ionizing radiation or arsenic. In addition, premalignant skin conditions (eg, solar keratoses or Bowen's disease) may have been present in the patients who developed epitheliomas after PCT. These conditions are difficult to diagnose in patients with severe psoriasis, and they might become obvious as the psoriasis clears upon PCT. (3 refs)

- 79-4862 Identifying and Treating Skin Malignancies. (Eng) Jessen, R. T. (Div. Dermatology, Univ. New Mexico Sch. Medicine, 2701 Frontier, NE, Albuquerque, NM 87131); Merwin, C. F. *Geriatrics* 34(6): 71-78; 1979.

The clinical presentation and treatment of skin malignancies are reviewed. Actinic keratoses are precancerous lesions that occur almost exclusively in fair-complexioned persons. Squamous cell carcinomas are found predominantly on sun-exposed areas; those arising in sun-damaged skin rarely metastasize, but those developing in sites of previous injury of chronic inflammation tend to metastasize. Bowen's disease is a squamous cell carcinoma that has not broken through the basement membrane into the dermis. The incidence of internal malignancies may be increased in Bowen's disease patients with lesions on non-sun-exposed areas of the body. Basal cell carcinomas are the most common skin cancers. They are locally invasive and rarely metastasize. Keratoacanthoma is a rapidly growing but usually self-involuting tumor. Malignant melanomas arise at the epidermal-dermal junction. Lentigo malignant melanomas have the best prognosis and nodular melanomas the poorest prognosis, especially tumors on the trunk. (21 refs)

- 79-4863 Relative Carcinogenic Effects of Different Mammography Techniques. (Eng) Muntz, E. P. (Dept. Radiology, Univ. Southern California, Los Angeles, CA 90033). *Med Phys* 6(3): 205-210; 1979.

Using recent data from the literature, a study was made of the significance of various assumptions concerning the appropriate measures for carcinogenesis in mammography and the shape of the dose-effects relationship. There is no way in principle to be "conservative" in a relative sense by assuming a given dose-response curve for the comparison of mammography techniques using different beam qualities. However, for nonextreme amounts of nonlinearity, there is typically no more than about a 20% max uncertainty for the entire mammography energy range. The uncertainties associated with the precise shape of the dose-effects relationship for carcinogenesis at low doses as well as the distribution of sensitive tissue in the breast make it difficult to select a best measure for the relative carcinogenic effects of different mammography techniques. The assumption of a linear dose-effects relationship favors the soft beam techniques, in comparison with dose-effects relationships with concave upward nonlinearities. The assumption of no "adipose shield" favors the hard beam techniques. The av dose per unit of entrance dose, which is directly proportional to the av carcinogenic effect for a linear effects relationship, can be determined for any breast thickness and composition. It is emphasized that although there is considerable uncertainty in specifying a reliable indicator of relative carcinogenic effects, the absolute risk can, with high probability, be conservatively estimated from a linear effect vs dose relationship used with an av dose. (10 refs)

- 79-4864 Urinary Bladder Carcinogenesis: Initiation-Promotion. (Eng) Cohen, S. M. (Dept. Pathology, St. Vincent Hosp., 25 Winthrop St., Worcester, MA 01604). *Semin Oncol* 6(2): 157-160; 1979.

A review of urinary bladder carcinogenesis in humans and animals is presented. A chemical etiology for bladder cancer (BC) was first suggested in 1895 in relation to aniline dyes. Since then, 2-naphthylamine, benzidine, 4-aminobiphenyl, N-2-acetylaminofluorene (AAF), N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN), N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), and N-methyl-N-nitrosourea (MNU) have been implicated. Studies of AAF revealed the necessity of activating carcinogens to reactive electrophilic intermediates capable of reacting with nucleic acids or proteins. BBN and FANFT are bladder-specific carcinogens in animals. Animal models are useful because the pathology and course of BC in animals are similar to those in humans: simple hyperplasia progressing to nodular and papillary hyperplasia, to benign-appearing tumors, and then to noninvasive and, finally, invasive carcinomas, sometimes with distant metastases. Humans are likely to be exposed to low doses

of several chemicals at once, and these may have an additive or synergistic effect. Some substances are not complete carcinogens but possess either initiator or promoter properties. Initiation is rapid, irreversible, and likely to be a somatic mutation, but promotion is slower, initially reversible, and is likely due to the phenotype expression of initiated cells. Initiation-promotion in BC has been shown for MNU-sodium saccharin, MNU-sodium cyclamate, FANFT-sodium saccharin, FANFT-DL-tryptophan, 4-aminobiphenyl-DL-tryptophan, 2-naphthylamine-DL-tryptophan, and FANFT-L-tryptophan. Substances in rat urine appear to be capable of promoting BC in heterotopic rat bladders. (22 refs)

- 79-4865 Radiation Hazards and Control in Nigeria. (Eng) Bandele, S. D. (Dept. Radiology, Ahmadu Bello Univ. Hosp., Zaria, Nigeria). *Radiography* 45(533): 97-99; 1979.

The health hazards of ionizing radiation in Nigerian hospitals, where there is no organized control of its use, are discussed. Direct effects include erythema, hair loss, and sterility. Ionization may also cause changes in the configuration of the affected cells, possibly leading to cancer. The ways in which ionizing radiation-induced mutation may represent a serious hazard to future generations are described. (no refs)

- 79-4866 Biology of Cancer. (Fre) Dulbecco, R. (Salk Inst., La Jolla, CA). *Recherche* 10(100): 434-442; 1979.

The general biological aspects and mechanisms of cancer are reviewed. Recent studies have demonstrated that the transformation of a normal cell into a tumor cell is due to a specific gene of a virus integrated in the chromosomes of the infected cell. This gene is believed to induce the synthesis of a particular enzyme, which plays a primary role in tumor cell growth. An identical mechanism can also be used to explain chemical and physical carcinogenesis. (8 refs)

- 79-4867 Discussion Summary. (Eng) Wilkie, N. M. (Medical Res. Council Virology Unit, Inst. Virology, Glasgow, Scotland). *IARC Sci Publ* 24(1): 149-153; 1978.

A discussion of papers presented at a session of a symposium on herpesviruses (HV's) is summarized. Topics covered include the general sequence arrangement in the genomes of several HV's, analysis of defective herpes simplex virus type 1 (HSV-1) genomes, DNA replication, marker rescue experiments and the mapping of crossover points in intertypic recombinants between HSV-1 and

HSV-2, plasmid forms of Epstein-Barr virus DNA. (no refs)

- 79-4868 Discussion Summary. (Eng) Becker, Y. (Lab. Molecular Virology, Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel). *IARC Sci Publ* 24(1): 423-427; 1978.

Papers presented at a symposium on herpesviruses (HV's) provided information on some of the molecular events occurring during the replication of three HV's [herpes simplex virus (HSV), cytomegalovirus, and Epstein-Barr virus] in permissive and nonpermissive cells. The data covered analysis of the viral genome, molecular events in lytically infected cells (transcription and translation of viral messenger RNA, control of viral DNA replication, recombination of HSV DNA), and semipermissive interactions of HV's with cells. (no refs)

- 79-4869 The Structural Proteins and Glycoproteins of Herpesviruses: A Review. (Eng) Spear, P. G. (Univ. Chicago, Chicago, IL); Sarmiento, M.; Manservigi, R. *IARC Sci Publ* 24(1): 157-167; 1978.

Available information concerning the role of herpesvirus-specified structural proteins and glycoproteins in the morphogenesis and function of the virion is reviewed. The virions of different herpesviruses are similar with respect to the number and kinds of constituent polypeptides, in spite of variability in the structures of the individual polypeptides. The total number of virion polypeptides and glycopeptides ranges from 20 to 30 for different viruses. In general, no more than one-fourth of these polypeptides are detectable in naked nucleocapsids, suggesting that most of the virion polypeptides are acquired during the process of envelopment. Although the functions of most individual structural proteins have not been identified, the nucleocapsid proteins appear to serve primarily structural roles or may mediate packaging of the viral genome. The nonglycosylated envelope proteins appear to play essential roles in the process of envelopment, and the glycoproteins, which are probably all exposed to the virion surface, appear to mediate adsorption to and penetration of the host cell. Two of the herpes simplex virus glycoproteins have been identified as targets of neutralizing antibodies and one of these proteins has been shown to mediate viral penetration, probably by promoting fusion between the virion envelope and cell surface membrane. (43 refs)

- 79-4870 Transformation of Non-lymphoid Cells by Herpesviruses: A Review. (Eng) Rapp, F. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA); Shillito, E. J. *IARC Sci Publ* 24(1): 431-450; 1978.

Cell types that become transformed following herpesvirus infection and their relationship to malignant disease are reviewed. Most mammalian cells can be transformed by herpes simplex virus (HSV), which is usually partially inactivated. Temperature-sensitive mutants of HSV can transform cells without prior inactivation. The transformed cells may show a fibroblastoid or epithelioid morphology. Oncogenic cells of the former type induce tumors resembling fibrosarcomas and oncogenic cells of the latter type give rise to tumors resembling adenocarcinomas. Cells transformed by HSV do not release virus particles but they do synthesize virus proteins. Immunization of hamsters with cells transformed by HSV do not, however, protect against tumor isografts. Human cytomegalovirus (CMV), which is widespread throughout the population, can transform human cells. Guinea pig herpeslike virus (GPHLV) induces morphological transformation in guinea pig WBC and nonlymphoid cells. After 37 passages in vitro, the transformed cells are able to induce metastasizing fibrosarcomas in hamsters. Epstein-Barr virus (EBV) has been shown to infect only human B lymphocytes, but EBV DNA has been found in epithelial cells derived from nasopharyngeal carcinomas. The EBV genome can be maintained and expressed in transformed hybrid cells with a nonlymphoid morphology. Lucke herpesvirus has been found in frog renal tumors, but since other viruses have also been isolated from the tumor extracts, there is no proof that this virus causes cell transformation and tumors. (76 refs)

- 79-4871 Discussion Summary. (Eng) Schaffer, P. A. (Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA). *IARC Sci Publ* 24(1): 577-580; 1978.

A discussion of papers presented at a session of a symposium on herpesviruses (HV's) is summarized. In a review of the transformation of nonlymphoid cells by HV's, the unavailability for study of human cell lines transformed by HV's and the fact that transplantation rejection antigens have not yet been identified in HV systems were stressed. The second major topic of the session concerned transformation of lymphoid cells by HV's and a comprehensive compendium of the characteristics of lymphoblastoid cell lines transformed by Epstein-Barr virus and other primate HV's. (no refs)

- 79-4872 Discussion Summary. (Eng) Pope, J. H. (Queensland Inst. Medical Res., Brisbane, Queensland, Australia). *IARC Sci Publ* 24(1): 655-656; 1978.

Papers presented at a symposium on herpesviruses (HV's) gave further evidence that a variety of HV's transform a variety of cells. The transformation should be regarded as being quite complex, and it may involve interactions bet-

ween several viruses, including possible endogenous C-type viruses. Changes in the biological properties of cytomegalovirus(CMV)-transformed cells, the effect of the physiological condition of the cells in CMV infection, and hazards that Epstein-Barr virus-infected cells may have to face before they become fully transformed were among the several other topics covered. (no refs)

- 79-4873 Comparison of Immune Responses and Viral Markers in Herpesvirus-associated Carcinomas: A Review. (Eng) Henle, W. (Div. Virology, Joseph Stokes, Jr. Res. Inst., Children's Hosp., Philadelphia, PA); Henle, G. *IARC Sci Publ* 24(II): 801-813; 1978.

The relationship of the following herpesviruses to their associated carcinomas is reviewed: Lucke tumor herpesvirus (LTHV), herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), and Epstein-Barr virus (EBV). LTHV antigens have been detected in cultures of renal adenocarcinomas of the frog. EBV DNA or antigens have been detected in biopsy specimens of human nasopharyngeal carcinomas (NPC). Similar relationships have not been demonstrated between HSV-1 or HSV-2 and cervical or other squamous cell carcinomas. Carcinomas have been induced in frog embryos with LTHV, and there are unconfirmed reports of uterine carcinoma induction in mice by HSV-2. Transformation of normal epithelioid cells has been attained with HSV-1 and HSV-2, possibly with LTHV, but not with EBV. Virus-specific serology has revealed distinct patterns and titers of antibodies to EBV-related antigens in NPC patients, and the findings correlate with the stage and prognosis of the disease. Suggestive serologic results have also been obtained with HSV-1 and HSV-2. The data indicate an etiological role of LTHV in the Lucke tumor and a causal or at least contributory role of EBV in NPC. The evidence for a relationship between HSV-2 and cervical carcinoma and between HSV-1 and squamous cell carcinomas of the head and neck is tenuous. (37 refs)

- 79-4874 Discussion Summary. (Eng) Evans, A. S. (Yale Univ., New Haven, CT). *IARC Sci Publ* 24(II): 795-797; 1978.

At a discussion held after a session of a symposium on herpesviruses (HV's), the levels at which different immune systems affect the spectrum of HV infections were reviewed. T cells appear to be the major cells involved in the control of primary and recurrent infections. Latent HV infections were defined and classified, the cells in which different HV's are latent identified, and the use of temperature-sensitive mutants in studying the biochemistry of the process described. Cell-mediated immunity to HV's develops in both natural and experimental infections;

cellular immunity is involved in the control of these primary infections. (no refs)

- 79-4875 Discussion Summary. (Eng) Munk, K. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany). *IARC Sci Publ* 24(II): 927-929; 1978.

A discussion of papers presented at one session of a symposium on herpesviruses (HV's) is reviewed. Papers on different host/HV systems, such as infections of fish, frogs, birds, and mammals (including humans), on the correlation between serological data and the clinical course of malignancies of possible HV etiology, and on viral markers in HV-associated lymphomas and host defenses against the oncogenic effects of lymphotropic HV were among the many covered. (no refs)

- 79-4876 Discussion Summary. (Eng) Frenkel, N. (Univ. Chicago, Chicago, IL). *IARC Sci Publ* 24(I): 261-265; 1978.

Studies presented at one session of a symposium on herpesviruses (HV's) concerned HV-specific antigens, and the findings are summarized under four headings: antigenic relatedness of HV's, purification of individual viral antigens, tumor-associated viral antigens, and functional studies of virus-specified polypeptides. (no refs)

- 79-4877 The Immunology of Primary and Recurrent Herpesvirus Infection: An Overview. (Eng) Nahmias, A. J. (Div. Infectious Diseases and Immunology, Dept. Pediatrics, Emory Univ. Sch. Medicine, Atlanta, GA); Ashman, R. B. *IARC Sci Publ* 24(II): 659-673; 1978.

The immunology of primary and recurrent herpesvirus infection is reviewed. It appears that many herpesviruses can be present in circulating leukocytes in a latent or infectious form. Herpetic infection induces numerous changes in the cell membrane, and the various antigens of the virus or virus-infected cells stimulate a multitude of humoral and cell-mediated responses. The latter may differ according to virus strain and may show cross-reactivity among different strains. Several common patterns in the immune responses to primary infection have been found. Antibodies of the Ig-M class are usually detected within 1-3 wk after infection and are usually of short duration. The persistence of IgG antibodies will depend on their reactivity to particular herpesvirus antigens: neutralizing antibodies generally persist longer than complement-fixing antibodies. IgE antibodies to herpes simplex viruses have been detected within 1 wk after infection in rabbits. Endogenous or exogenous recurrences may help maintain antibody levels. It is not

REVIEW

possible at present to pinpoint which of the various effector systems is the crucial one in determining the outcome of a primary infection. (65 refs)

- 79-4878 Persistent, Chronic, and Latent Infections by Herpesviruses: A Review. (Eng) Stevens, J. G. (Reed Neurological Res. Center, Dept. Microbiology and Immunology, Univ. California, Sch. Medicine, Los Angeles, CA). *IARC Sci Publ* 24(II): 675-685; 1978.

Persistent, chronic, and latent infections by herpes simplex virus (HSV), Epstein-Barr virus (EBV), and the Lucke agent (LV) are reviewed. HSV appears to establish latent infections which are selectively maintained in neurons. The form in which the viral genome persists in these cells and how the infection is maintained over time is not understood. Latent EBV is maintained in neoplastic B-lymphocytes and probably in normal and malignant epithelial cells of the nasopharynx as circular extrachromosomal DNA and DNA linearly integrated into cellular chromosomes, respectively. Virus-specific antigens in latently-infected cells include EBV nuclear antigen and membrane antigen. Latent LV is harbored in neoplastic kidney epithelial cells at temperatures $>12^{\circ}\text{C}$. The physical state of the latent virus is unknown, but it is known that membrane antigen is specified in latently infected cells. Permissive cells in vivo include essentially all cell types for HSV, epithelial cells of the nasopharynx and possibly B-lymphocytes for EBV, and neoplastic kidney epithelial cells at temperatures $<12^{\circ}\text{C}$ for LV. (42 refs)

- 79-4879 Similarities and Differences Between Various Herpesviruses: A Review. (Eng) Deinhardt, F. (Max V. Pettenkofer-Inst. Hygiene and Medical Microbiology, Univ. Munich, Munich, W. Germany); Wolf, H. *IARC Sci Publ* 24(I): 169-175; 1978.

The provisional classification of herpesviruses proposed by the Herpesvirus Study Group of the International Committee for the Nomenclature of Viruses is reviewed. Most animal species harbor their own herpesviruses of the alpha, beta, and possibly gamma groups. There is at least a partial antigenic cross-reactivity and partial DNA homology among the viruses within individual groups, whereas there are no similar relationships between the viruses of different groups. The gamma herpesviruses of primates all share some common antigen among themselves and with the human Epstein-Barr virus (EBV), they are all associated with B-lymphocytes, they do not cause lytic infections in nonlymphocytic cells, and their DNAs show a 30%-60% homology with EBV DNA. On the basis of their biological behavior, it is possible to distinguish between EBV strains which can lytically infect but not transform and those which can transform or lytically infect. Knowledge is lacking concerning the pathogenic mechanisms operative in the

different virus host-cell and virus host-organism interactions. At least part of the pathogenesis of EBV infections is certainly host and not virus controlled. (14 refs)

- 79-4880 Interaction of Oncornaviruses and Herpesviruses: A Hypothesis Proposing a Co-carcinogenic Role for Herpesviruses in Transformation -- A Review. (Eng) Hampar, B. (NCI Frederick Cancer Res. Center, Frederick, MD); Boyd, A. L. *IARC Sci Publ* 24(II): 583-589; 1978.

The interaction of herpesviruses and oncornaviruses and the role of C-type viruses in malignant transformation by herpesviruses are reviewed. Based on studies of BALB/c cells infected with herpes simplex virus (HSV), any oncogenic potential of HSV can best be explained by its role as a cocarcinogen. It is suggested that transformation by HSV and other putative cocarcinogens occurs in a manner similar to, if not identical to, spontaneous transformation. Two components are hypothesized as essential for transformation by cocarcinogens: an available genome for integration, and an accessible site for its integration into the cell genome. The cocarcinogen is postulated to induce repairable damage to the cell DNA, making sites accessible for integration of the type-C genome. Transformation of cells not actively producing type-C virus would require that the cocarcinogen induce both type-C virus synthesis and repairable DNA damage. Transformation by UV-irradiated HSV was studied in vitro using BALB/c cells. Activation of type-C virus by UV-irradiated HSV occurred at a frequency of approx $1-5 \times 10^5$. Transformation was observed only in cultures with activated type-C virus, and it occurred in a gradual and stepwise fashion. Periodic testing of transformed cells showed no evidence of spontaneous synthesis of an ecotropic type-C virus capable of forming a chronic infection. HSV antigens were demonstrated in the transformed cells by the fluorescent antibody method. (16 refs)

- 79-4881 Herpesvirus-associated Epidermal Hyperplasia in Fish (Carp). (Eng) Sonstegard, R. A. (Dept. Microbiology, Univ. Guelph, Guelph, Ontario, Canada); Sonstegard, K. S. *IARC Sci Publ* 24(II): 863-868; 1978.

The occurrence of herpesvirus-associated epithelial proliferations in carp (*Cyprinus carpio*) is reviewed. The tumors, which appear to be benign, are found on the skin, fins, eyes, and gills. Large numbers of herpesviruslike particles have been found associated with the proliferations, and the tumors are readily transmitted by rubbing tumor tissue against abraded epithelium of normal carp or by holding normal carp in the same tank as infected fish. No evidence of in vitro transformation has been detected in established fish cell lines, and attempts to establish a cell

line from the tumor cells have been unsuccessful. A similar tumor has also been described in European carp and in feral and laboratory-infected carp-goldfish hybrids, but there is no evidence that the tumor has spread to other North American fish species. The disease provides a unique opportunity to study genetic "drift" in herpesvirus. (14 refs)

- 79-4882 Co-carcinogenic Events in Herpesvirus Oncogenesis: A Review. (Eng) de The, G. (International Agency Res. Cancer, Lyon, France). *IARC Sci Publ* 24(II): 933-945; 1978.

Cocarcinogenic events in herpesvirus oncogenesis are reviewed. Both genetic and environmental factors play a determining role in the naturally occurring frog and chicken herpesvirus-associated tumors. Cofactors affecting the development of renal carcinomas in leopard frogs are temperature, degree of crowding, and age at the time of infection. Marek's disease (MD) in chickens is influenced by genetic constitution of the bird, sex, age at infection, stress, coccidiosis, and possibly avian oncornaviruses. MD viruses differ in oncogenic potential, natural infection with an apathogenic virus providing protection against later exposure to a pathogenic strain. Cell-mediated immunity appears to control the resistance of mice to herpes simplex virus (HSV) infection, resistance being a dominant trait. The most critical factor in oncogenesis by herpesvirus ateles (HVA) and herpesvirus saimiri in other than their natural hosts also appears to be genetically determined resistance or susceptibility. Three human tumors are associated with herpesviruses: cervical carcinoma (HSV type 2), Burkitt's lymphoma [Epstein-Barr virus (EBV)], and nasopharyngeal carcinoma (EBV). Malaria is also implicated in the etiology of Burkitt's lymphoma, and genetic factors or chemical carcinogens may play a role in nasopharyngeal carcinoma. (41 refs)

- 79-4883 Summary of Research in Primate Oncogenic Herpesviruses. (Eng) Deinhardt, F. (Max v. Pettenkofer-Inst. Hygiene and Medical Microbiology, Univ. Munich, Munich, W. Germany). *IARC Sci Publ* 24(II): 1087-1088; 1978.

Two groups of oncogenic simian herpesviruses have been identified to date. Both the Epstein-Barr virus-like viruses, restricted to Old-World nonhuman primates and always associated with B-lymphocyte markers, and the herpesviruses of New-World monkeys, associated with T-cell markers, are nononcogenic in their natural hosts but induce lymphoproliferative disease in related species. High priority areas for future research are listed, and the problems involved in procuring experimental animals are discussed. (no refs)

- 79-4884 Cell-Free Systems for In Vitro Translation of Herpes Simplex Virus Messenger RNA. (Eng) Preston, C. M. (Medical Res. Council, Inst. Virology, Glasgow, Scotland). *IARC Sci Publ* 24(I): 347-351; 1978.

A cell-free system active in translation of HSV (herpes simplex virus) messenger RNA was obtained by fractionation of reticulocyte lysates. Polysomes engaged in protein synthesis were removed from the lysate by rapid centrifugation; the supernatant from this procedure was concentrated by precipitation at pH 5, and ribosomal salt-wash proteins were added to the pH 5 fraction. Endogenous protein synthesis was further reduced by preincubation with micrococcal nuclease, although this treatment did not affect the translation of infected (or uninfected) BHK cell RNA. Polypeptides synthesized by the fractionated reticulocyte cell-free system were very similar to those produced by unfractionated reticulocyte lysates. (6 refs)

- 79-4885 Human Herpesvirus 1 as a Model of Regulation of Herpesvirus Macromolecular Metabolism: A Review. (Eng) Roizman, B. (Marjorie B. Kovler Viral Oncology Labs., Univ. Chicago, Chicago, IL); Morse, L. S. *IARC Sci Publ* 24(I): 269-297; 1978.

The replication of herpesviruses, particularly regulation of the viral gene product synthesis of herpes simplex viruses (HSV) types 1 and 2, is reviewed. The major criterion for defining polypeptides (pp's) as virus-specific is that their rate of synthesis increases after infection. Current evidence indicates that viral pp's form at least three groups (α , β , and γ) whose synthesis is coordinately regulated and sequentially ordered in a cascade fashion. The structural (virion) pp's comprise the largest and perhaps only component of the γ group. The synthesis of α pp's appears to require only the presence of DNA capable of initiating infection in permissive cells. The transition from α to β pp synthesis requires de novo transcription of viral DNA and the participation of functional α pp's; the synthesis of α pp terminates in the cytoplasm and requires functional β pp's. α and β messenger RNA do not compete for a common cytoplasmic factor, since the synthesis of the corresponding pp's is not mutually exclusive. The requirements for the transition from β to γ pp synthesis are similar to those for α to β . Viral DNA appears to be transcribed principally by host RNA polymerase II. The extent of transcription appears to be under some temporal control, and the abundance of transcripts generated from different regions of viral DNA is also controlled. Viral pp's probably modify transcription by interacting with the template-polymerase complex. The transition from α to β to γ RNA synthesis involves (1) the appearance in the cytoplasm of RNA suitable for translation of pp's comprising the next group and a cytoplasmic event that ends the synthesis of the previous group. Possible factors regulating the translocation of the RNA to the cytoplasm are discussed. There appears to be a clear segregation of templates specifying α pp's in HSV

REVIEW

DNA, whereas the templates for β and γ pp's appear to be randomly distributed. (64 refs)

- 79-4886 Herpesvirus in Humans. (Ger) Conner, B. (Medical Microbiology Dept., Ohio State Univ. Coll. Medicine, Columbus, OH 43210); Glaser, R. *Hautarzt* 30(6): 331-336; 1979.

Herpesviruses that cause diseases in humans (herpes simplex, varicella zoster, cytomegalovirus, and Epstein-Barr virus) share several characteristics, such as the ability to be latent and, later, reactivated and to cause immune reactions during the entire life-span of the host. These viruses have been implicated in the etiology of some malignant diseases. Attenuated viruses prepared for use in vaccinations may retain their oncogenicity. (32 refs)

- 79-4887 Characterization of Human Varicella-Zoster Virus DNA. (Eng) Hyman, R. W. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA); Iltis, J. P.; Oakes, J. E.; Rapp, F. *IARC Sci Publ* 24(1): 87-96; 1978.

The DNA of varicella-zoster virus (VZV) was isolated from infected hamster embryo lung cells by release into the Hirt supernatant and characterized by sucrose gradient sedimentation, restriction enzyme cleavage with either *EcoRI* or *HindIII* site-specific endonucleases, and by isopycnic banding in cesium chloride. The DNA's from different clinical isolates were compared. DNA's from VZV's isolated from either varicella or herpes zoster were indistinguishable on the basis of size and restriction enzyme cleavage pattern. The most important finding was that the buoyant density in cesium chloride of the VZV DNA isolated from varicella was reproducibly slightly lower than that of the VZV DNA isolated from herpes zoster. (16 refs)

- 79-4888 Elusive Search: Do Viruses Cause Human Cancer? (Eng) Consigli, R. A. (Div. Biology, Kansas State Univ., Kansas City, KS); Center, M. *J Kans Med Soc* 80(6): 341-342; 1979.

Evidence for and against the involvement of viruses in cancer etiology is reviewed. Viruses with considerable homology to simian virus 40 transform human cells in culture. Epstein-Barr virus has been found in nasopharyngeal carcinoma and Burkitt's lymphoma. Retrovirus particles have been isolated from the culture fluids of a malignant lymphoma cell line, and there is some evidence for the presence of retroviruslike particles in human mammary tumors. The greatest obstacle in proving

that a virus causes cancer are postulates requiring isolation of the agent from all infected organisms and induction of the disease in humans by a pure preparation. (no refs)

- 79-4889 Epstein-Barr Virus Genomes and their Biological Functions: A Review. (Eng) zur Hausen, H. (Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Freiburg im Breisgau, W. Germany); Fresen, K. O.; Bornkamm, G. W. *IARC Sci Publ* 24(1): 3-10; 1978.

Recent work on the organization of Epstein-Barr virus (EBV) DNA is reviewed. Multiple copies (1-200) of EBV DNA are commonly present in nonproducer cell lines transformed by this virus, and there are strain variations in different EBV isolates. The structural organization of the EBV genome derived from different cell lines remains to be elucidated. Partial denaturation mapping indicates some variability in the terminal sequences of EBV, and molecular biological studies reveal heterogeneities in DNA preparations from different EBV strains. P3HR-1 cells, at least, contain two subtypes of the EBV genome that, upon coinfection, complement each other in early antigen induction. A number of transforming EBV strains may be helper-dependent in some early and late functions and may require complementation by an as yet poorly defined component in P3HR-1 cells. (24 refs)

- 79-4890 Comparison of Humoral and Cell-mediated Responses and Virus Markers in Herpesvirus-associated Lymphomas: A Review. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden). *IARC Sci Publ* 24(11): 815-833; 1978.

The humoral and cell-mediated responses and virus markers in herpesvirus-associated lymphomas are reviewed. There is evidence that the Epstein-Barr virus (EBV) receptor is restricted to B lymphocytes and is either identical to or sterically closely associated with the C3 receptor of this particular target. However, there is no relationship between C3-binding and EBV-binding activities per se. It is possible that there is some relationship between the attachment of EBV to the EBV/C3 receptor and its action as a B-lymphocyte activating agent. In addition to viral antigen induction, with EB nuclear antigen as the main marker, EBV also induces profound changes in cellular behavior and biology. Serologically detectable, disease-related changes are largely restricted to the membrane antigen (MA) and early antigen (EA) complexes of the EBV system. MA/antibody complexes may be related to the risk of recurrence of disease. Anti-MA antibodies may act directly on their targets or via an antibody-dependent lymphocytotoxicity mechanism. The lymphocyte-detected MA is a different and probably more important target. The presentation of EA to the immune system by cells involved

in the proliferative disease process appears to be important for the induction of anti-EA antibodies in ongoing, EBV-related disease. Anti-EBNA antibodies are the last to appear in the course of acute primary EBV infection. Killer T cells appear during the acute phase of infectious mononucleosis (IM) and as a small minority in Burkitt's lymphoma and nasopharyngeal carcinoma. Neither peripheral, IM-associated, nor tumor-infiltrating EBV-specific killer T cells show evidence of syngeneic (HL-A) restriction. Animal studies of major histocompatibility complex restriction suggest that the phenomenon is largely determined at the level of macrophage T-cell interaction at the time of antigen presentation. EBV-specific killer T cells are probably not responsible for the long-term control of EBV-converted B cells. In the Marek's disease virus system, T cells serve as the targets of neoplastic transformation and also appear to play a role in host defense. (69 refs)

- 79-4891 Transformation of Lymphoid Cells by Herpesviruses: A Review with Special Reference to the Phenotypic Properties of Transformed Cells. (Eng) Nilsson, K. (Dept. Tumor Biology, Wallenberg Lab., Univ. Uppsala, Uppsala, Sweden). *IARC Sci Publ* 24(1): 451-472; 1978.

The in vitro transformation of lymphocytes by herpesviruses, particularly Epstein-Barr virus (EBV), is reviewed. EBV is a lymphotropic virus in vitro, its principal target cell being an EBV receptor- and complement receptor-expressing B lymphocyte. Lymphocytes from nonprimate species are resistant to EBV infection. Most of the cells from EBV-carrying lymphoblastoid cell lines (LCL) are derived from cells infected in vitro, the interaction between virus and host cell genomes in these cells being such that virus replication is prevented. LCL and Burkitt's lymphoma (BL) lines typically contain 10-100 copies of the EBV genome. Several antigenic changes have been detected in lymphocytes immortalized by EBV, but even in most producer lines the fraction of cells replicating virus is very small. The BL cell generally resembles a resting B lymphocyte, whereas the LCL cell has many similarities to mitogen-stimulated B lymphoblasts. LCL are normal diploid cells that are nontumorigenic in nude mice, whereas BL lines are aneuploid and tumorigenic. The cell lines also differ in their surface glycoprotein patterns. Herpesvirus papio and the chimpanzee agent seem to be closely related to EBV, and the lymphoid cell lines carrying these viruses are similar to those of human EBV-carrying lines, especially the LCL type. Thus, these viruses may be better models for the study of EBV-associated diseases in humans than herpesvirus saimiri, herpesvirus ateles, or Marek's disease virus. (108 refs)

- 79-4892 The Role of Herpes and Papilloma Viruses in Human Tumors. (Ger) zur Hausen, H.

(Institut für Virologie, Zentrum für Hygiene der Universität, Hermann-Herder-Str. 11, D-7800 Freiburg, W. Germany). *Munch Med Wochenschr* 121(24): 811-812; 1979.

Studies of the role of herpes and papilloma viruses in human tumors are reviewed. Epstein-Barr virus plays a role in Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC), but the nature of its role is not yet known. The role of herpes simplex virus type 2 in carcinoma of the vulva, uterine cervix, and penis and the role of papilloma virus in condyloma acuminata are also unclear. Transformation of epidermodysplasia verruciformis into squamous epithelial carcinoma in light-exposed areas is observed only in warts caused by a certain type of human papilloma virus. (2 refs)

- 79-4893 Integration of Epstein-Barr Virus DNA. (Eng) Lindahl, T. (Dept. Chemistry and Tumor Biology, Karolinska Institutet, Stockholm, Sweden); Adams, A.; Andersson-Anvret, M.; Falk, L. *IARC Sci Publ* 24(1): 113-123; 1978.

Techniques that have been employed to study integration of tumor virus DNA are reviewed and their potential application to Epstein-Barr virus (EBV)-transformed cells is discussed. Sucrose gradient or glycerol gradient centrifugation provided early evidence for the existence of nonintegrated EBV DNA in transformed cells, but not for covalently closed circular EBV DNA or integrated EBV DNA. Neutral cesium chloride density-gradient centrifugation is the best technique presently available to analyze EBV DNA integration. Alkaline cesium chloride density-gradient centrifugation is a less satisfactory technique. Centrifugation in cesium chloride gradients containing antibiotics or dyes seems useful for verifying results obtained by regular cesium chloride density-gradient centrifugation and for demonstrating that the integrated EBV DNA exhibits unusual banding properties. The Hirt fractionation method has been used to confirm the absence of detectable amounts of circular EBV DNA in the human lymphoma cell line AW-Ramos, which contains only one linearly integrated EBV genome-equivalent per cell. The network technique is complicated by artefacts but may be used to yield information similar to that provided by the Hirt technique. Other methods include determination of the fate of parental virus DNA after infection, and restriction endonuclease treatment of DNA from virus-transformed cells followed by gel electrophoresis. There is a shortage of good methods to analyze integration of high mol wt viral DNA. Integrated EBV DNA has been found in Burkitt's lymphoma-derived cell lines, but its significance in relation to the "transformed state" of cells is unclear. (40 refs)

- 79-4894 The Epstein-Barr Virus. (Eng) Henle, W. (No affiliation given). Henle, G.; Lennette, E. T. *Sci Am* 241(1): 48-59, 162; 1979.

The prime candidate for a virus involved in human cancer is Epstein-Barr virus (EBV). EBV has been observed in Burkitt's lymphoma (BL) cells, and the antibody (Ab) titer to EBV in children with BL is eight- to tenfold higher than that in healthy children. EBV also appears to be intimately associated with nasopharyngeal carcinoma (NPC), and it is unequivocally the etiologic agent for infectious mononucleosis (IM). After EBV infection, the virus persists in a latent stage in the B lymphocytes, and it is periodically activated and released in the saliva. EBV has been shown to transform human B lymphocytes in vitro and in vivo. EB nuclear antigen (Ag) is the only Ag present in EBV-infected nonproducer cells. When such cells are induced to enter the lytic cycle, several additional Ag's are produced and progeny virus particles are liberated. The sequence of events following infection with EBV in humans is less clear, as is the significance of observed differences in the Ab profiles of infants and adults with EBV infections. The case for a causal relationship between EBV and BL and NPC is reviewed. About 80% of American and 2% of African cases of BL are not associated with EBV, but it is likely that when the virus is present, it is either a primary or priming factor in the disease. (no refs)

79-4895 Infectious Mononucleosis. (Eng) Rodriguez-Lopez, F. (Dept. Pediatrics, Sch. Medicine, Univ. Murcia, Murcia, Spain). *Paediatrician* 8(1/2): 48-55; 1979.

The etiology, pathogenesis, epidemiology, diagnosis, complications, and treatment of infectious mononucleosis are reviewed. The discovery of antibodies against Epstein-Barr virus in patients with mononucleosis confirmed its viral etiology and demonstrated a relationship between infectious mononucleosis and Burkitt's lymphoma. (9 refs)

79-4896 Pathogenesis of Infectious Mononucleosis. Burkitt's Lymphoma and Nasopharyngeal Carcinoma: A Unified Scheme. (Eng) Pagano, J. S. (Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC); Okasinski, G. F. *IARC Sci Publ* 24(II): 687-697; 1978.

The pathogenesis of infectious mononucleosis (IM), Burkitt's lymphoma (BL), and nasopharyngeal carcinoma (NPC) is reviewed and a unified scheme presented. In NPC, infection with Epstein-Barr virus (EBV) probably begins in the throat. Replication would proceed after circulation of the linear EBV genome; and in some cases, replication of the circular DNA template would become arrested, and the EBV plasmid would become established. A plasmid-bearing epithelial cell may be the nonmalignant progenitor of NPC. The final step probably involves insertions of EBV genes that code for transforming functions. The genetic predisposition to this malignancy may be

evidenced in a kinetic rather than a mechanistic fashion. In BL, EBV in epithelial cells would move to lymphoid cells after being shed in the mid-pharynx. This is the nonmalignant phase of the infection, with the infected lymphoid cell as the progenitor of BL. After the insertions of specific EBV genes have occurred, a monoclonal malignant transformation might ensue. Geographical rather than genetic events dispose to the ultimate outcome of the lymphoma; in addition, a failure of specific cell-mediated immunity almost certainly affects lymphoma development. Primary infection of epithelial cells and secondary infection of B-lymphocytes also occurs in IM. The viral DNA forms the EBV plasmid and induces a cellular proliferation of the B-lymphocytes which resembles malignant transformation. Random insertions of pieces of EBV DNA in the cellular DNA probably occur. The distinction between transformed (BL) and proliferating (IM) cells might have a basis in the function of the plasmid, with IM cells under its direction and BL cells under the direction of the inserted genes. Based on this scheme, one might predict that other malignancies whose association with EBV is as yet unrecognized may exist. (47 refs)

79-4897 Portraits of Viruses: The Poxviruses. (Eng) Fenner, F. (Centre Resource and Environmental Studies, Australian Natl. Univ., PO Box 4, Canberra, ACT 2600, Australia). *Intervirology* 11(3): 137-157; 1979.

This review of the use of poxviruses in the development of virology includes the classification and nomenclature of viruses, the particulate nature of viruses, the morphology and chemistry of animal viruses, the artificial propagation of animal viruses, the assay of viral infectivity, reactivation and intramolecular recombination, inclusion bodies and viral carcinogenesis, the pathogenesis of generalized viral infections, humoral and cell-mediated immunity, myxomatosis of rabbits, and the irradiation of smallpox. For a period in the 1930's and again in the 1960's, poxviruses were used as tumor-producing agents in studies of carcinogenesis. (156 refs)

79-4898 Hepatitis B Virus and Hepatocellular Carcinoma (Letter to Editor). (Eng) Trichopoulos, D. (Dept. Hygiene and Epidemiology, Univ. Athens Medical Sch., Goudi, Athens 609, Greece). *Lancet* 1(8127): 1192; 1979.

Several points in a previous paper on the association between hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) are clarified. The purpose of the paper was to evaluate the association of HBV with HCC in general, rather than with specific subgroups of it (ie, HCC with underlying alcoholic cirrhosis). If HBV causes cirrhosis and cirrhosis leads to HCC, it is indeed sufficient reason to indict HBV as a cause of HCC, as most epidemiologists would agree. (7 refs)

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- 79-4899 Retrodifferentiation and the Fetal Patterns of Gene Expression in Cancer. (Eng) Uriel, J. (Institut de Recherches Scientifiques sur le Cancer, B. P. 8, 94800 Villejuif, France). *Adv Cancer Res* 29: 127-174; 1979.

Retrodifferentiation (RD) and fetal patterns of gene expression in cancer are reviewed. Fetal patterns in malignant tumors (tumor-associated antigens, enzyme activities and metabolic changes, isozymes, and morphologic and structure-dependent properties), fetal patterns in non-cancerous growth (fetal antigens in regeneration, cell injury, and tissue repair, fetal isozymic transitions, and morphologic changes), the plasticity of the differentiated state (differentiation vs RD, differentiation of malignant cells, RD in cell injury and tissue repair, and RD in normal and transformed cells in vitro), and RD and cancer are the topics covered. It appears that RD is a physiological and common adaptive process for the maintenance of cell integrity against deleterious agents (physical, chemical, and viral). In physiological conditions, RD is counterbalanced by redifferentiation. The studies reviewed suggest that the resemblance between many cancerous and embryo-fetal cells is significant, since it stems from the convergence of common antigenic, biochemical, morphologic, and behavioral properties; that the resemblance is, nevertheless, not specific to neoplasia but is also seen in some noncancerous cells; and that RD seems to be a unique mechanism of cell rejuvenation underlying neoplastic development and regenerative processes. It is emphasized that many properties of cancerous cells may result in part from an adaptive process against deleterious internal factors (aging, abnormal metabolism, or biosynthetic errors) or noxious external agents (chemical, physical, viral, or mutational) and that RD appears to be the most efficient mechanism underlying the adaptive process. (200 refs)

- 79-4900 Neoplasias and B-Cell Precursors. (Eng) Seligmann, M. (INSERM Unit Immunopathology, Hopital Saint Louis, Paris, France). *Nature* 279(5714): 578; 1979.

Various studies suggest that clonal diversification is accomplished by the pre-B-cell stage in the B-cell differentiation pathway. In myeloma patients, antibodies specific for idiotypic determinants of the myeloma globulin stain bone marrow cells with pre-B-cell characteristics, which provides evidence that pre-B cells belong to the neoplastic clone. Some murine and human neoplasias involve early B-cell precursors that produce cytoplasmic immunoglobulin in the absence of membrane-bound immunoglobulin molecules. (16 refs)

- 79-4901 Hairy-Cell Leukemia. (Ita) Carbone, A. (Istituto di Anatomia, Università Cattolica del

Sacro Cuore, Rome, Italy); Lauriola, L.; Piantelli, M.; Salsano, F.; Mango, G.; Musiani, P. *Recent Prog Med* 66(4): 370-381; 1979.

The recent literature on hairy cell leukemia (HCL) is reviewed. HCL affects mainly adults above 50 yr; the men-to-women ratio is 4:1. Splenomegaly is always present, and moderate hepatomegaly is seen in about half of all cases. Lymph node involvement is rare. Pancytopenia, normocytic and normochromic anemia, and hairy cells accounting for 15%-90% of the WBC are characteristic of HCL. The hairy cells possess intrinsic membrane immunoglobulins. The response of hairy cells to mitogens (phytohemagglutinin concanavalin A, and pokeweed mitogen) is reduced compared to normal controls. The findings indicate the B-lymphocyte nature of HCL. (40 refs)

- 79-4902 Influence of the Major Histocompatibility Complex on T-Cell Activation. (Eng) Miller, J. F. (Walter and Eliza Hall Inst. Medical Res., Post Office Royal Melbourne Hosp., Victoria, Australia). *Adv Cancer Res* 29: 1-44; 1979.

The effects of the major histocompatibility complex (MHC) gene products on T lymphocytes and on tumor resistance are reviewed. The MHC-linked *Ir* genes control T-cell activities and T-cell-dependent functions, and the reactivities of various T-cell subsets are restricted by distinct MHC genes. I-region gene products govern the immune responses of helper T cells and T cells involved in delayed hypersensitivity to antigens presented by macrophages and B cells. H-2K and H-2D gene products influence the response of T cells that are directly cytotoxic and that play an essential role in resistance to virus infections. The exact manner by which the MHC produces such effects is not known, but several possible mechanisms have been proposed. One suggestion is that MHC gene products are intimately involved in delivering an activating signal to T cells. Only antigenic determinants able to associate with such products would be immunogenic. The existence of several MHC gene loci and of multiple allelism at each locus will ensure effective association of antigenic determinants with MHC gene products in most members of a given species. Polymorphism thus allows most individuals to respond adequately to one or other determinant of a complex antigen. (150 refs)

- 79-4903 Suppressor Cells: Permitters and Promoters of Malignancy? (Eng) Naor, D. (Lautenberg Center for General and Tumor Immunology, Hebrew Univ.--Hadassah Medical Sch., Jerusalem, Israel). *Adv Cancer Res* 29: 45-125; 1979.

The role of suppressor (SP) cells in the development of malignancy is reviewed. Studies demonstrating the

augmentation of antitumor responses in experimental immunocrippled animals (adult thymectomized, splenectomized, x-irradiated, or antithymocyte serum-inoculated) are described briefly. Most of these studies were performed before the function of SP cells was recognized, but a retrospective picture of these findings may be interesting, since at least part of the results may be interpreted differently if the function of the SP cell is taken into account. The possibility that SP cells are the initiators of immunostimulation and sneaking through phenomena is also surveyed. More-direct experimental evidence showing the effect of specific and nonspecific SP cells on the relationships between the tumor and host immune system is presented. For the most part, the effect of SP cells on syngeneic tumors and, occasionally, on nonspecific tumor cells is covered. Nonspecific neoplastic cells cannot stimulate a detectable allogeneic immune response after inoculation into an allogeneic host, and they can grow progressively in such an environment. SP cells are classified arbitrarily into permissive SP cells, which populate the host before its confrontation with the tumor, and promoter SP cells, which are induced by the tumor. Finally, chemical, physical, and biological properties of these SP cells are described, and various means for their selective elimination are offered. SP cells can be eliminated from potential or actual tumor-bearing hosts by adult thymectomy, splenectomy, or hydrocortisone acetate or antithymocyte serum treatment, but these methods may induce a general autoimmune response in addition to antitumor activity. (230 refs)

- 79-4904 Immunosuppression in Clinical Organ Grafting. (Eng) Calne, R. Y. (Dept. Surgery, Univ. Cambridge Clinical Sch., Hills Road, Cambridge CB2 2QQ, England). *Trends Pharmacol Sci* 1(Inaug. Issue): 21-22; 1979.

A new immunosuppressive drug currently being tested is Cyclosporin A (CyA), a cyclic fungal peptide of 11 amino acids, 1 of which is unique. Apparently, it acts in a manner completely different from that of any other immunosuppressive drug. It affects proliferating T cells, and the serum of treated animals and patients inhibits phytohemagglutinin transformation and mixed lymphocyte culture responses. It is not known why CyA is so specific in affecting transforming lymphocytes. (18 refs)

- 79-4905 Concanavalin A Receptors on the Surface Membrane of Lymphocytes from Patients with Burkitt's Lymphoma, Other Malignant Lymphomas, Leukaemia and Lymphoma Cell Lines. (Eng) Ben-Bassat, H. (Chanock Center Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Goldblum, N. *IARC Sci Publ* 24(11): 639-647; 1978.

The mobility of concanavalin A (Con A) receptor sites on

lymphocytes from patients with malignant lymphomas and chronic lymphocytic leukemia (CLL) was studied. Lymphocytes from the peripheral blood and tumor tissues of patients with African Burkitt's lymphoma (BL) showed reduced cap-forming ability and increased agglutinability in response to con A, compared with normal lymphocytes. Blood lymphocytes from patients with CLL, Hodgkin's disease, and other malignant lymphomas showed a similar reduction in cap formation and increase in agglutination, compared with lymphocytes from normal subjects, patients with carcinoma, and patients with nonmalignant disorders. The cap formation of lymphocytes from a healthy donor or a lymphoma patient was independent of the source from which the cells were isolated, eg, lymph-node, spleen or blood. Lymphoma cell lines established from tumors of BL patients and lymphoblastoid cell lines originating from other sources also exhibited an increased agglutination and reduced cap formation with con A. Further studies indicated that Epstein-Barr virus-positive human lymphoid lines had a lower cap-forming ability than virus-negative lines. (12 refs)

- 79-4906 Second Malignant Neoplasms in Hodgkin's Disease. (Eng) Getaz, E. P. (S. E. Massachusetts Medical Associates, 322 E. Center St., W. Bridgewater, MA 02379). *Cancer Chemother Pharmacol* 2(3): 143-145; 1979.

The prolonged survival of patients with Hodgkin's disease (HD) brought about by combined chemotherapy (approx 75% of all patients with advanced HD achieve complete remission) has led to the recognition of an increased risk of second tumor induction. The features of this induction are reviewed. The severe depression of cellular immunity that accompanies HD may be a contributing factor in the development of subsequent neoplasms. A variety of second tumors in HD patients has been documented, but their possible significance was overlooked because the incidences of the tumors (apart from skin tumors) seemed no greater than those expected in the general population. More recent reports have shown significant incidences of acute nonlymphocytic leukemia and anaplastic carcinoma of the thyroid in HD patients, and there is also an unexplained increase in Kaposi's sarcoma. The etiology of second malignancies is multifactorial. The effects of immunosuppressive treatment for HD augments the patients' own impaired cellular immunity, providing a receptive milieu for the oncogenic effects of radiation and chemotherapeutic agents. The incidence of second tumors is also related to the intensity of HD treatment, except for thyroid carcinomas, in which the response may be biphasic. (37 refs)

- 79-4907 Immunology of Rat Hepatic Neoplasia. (Eng) Baldwin, R. W. (Cancer Res. Labs., Univ. Nottingham, Nottingham, England). *Prog Biochem Pharmacol* 14: 109-122; 1978.

The immunology of rat hepatic cancer is reviewed. Carcinogen-induced rat hepatic neoplasms express a variety of neoantigens, the most consistently demonstrable components being the tumor-associated embryonic antigens. These have been demonstrated on all of the hepatic tumors analyzed so far, including both primary and transplanted tumors induced with aminoazo dyes and 2-acetylaminofluorene-induced tumors. Typing of these antigens may provide suitable methods for characterizing transformed cells. Antigen assay may also provide simple screening systems for the preliminary evaluation of chemical carcinogens. The most significant characteristic of carcinogen-induced tumors is the expression of tumor-specific cell surface antigens that may function as tumor-rejection antigens. This type of neoantigen is not always expressed on transformed cells, however. These neoantigens are highly polymorphic and, in most instances, it has been shown that tumors express individually distinct components. The tumor cell surface products may be modified histocompatibility antigens. It is suggested that they can be utilized for the analysis of "mutationlike" events in hepatocarcinogenesis. (50 refs)

- 79-4908 **The Micronucleus Test: Statistical Design and Analysis.** (Eng) Mackey, B. E. (U.S. Dept. Agriculture, Science and Education Admin., Western Regional Res. Center, Berkeley, CA 94710); MacGregor, J. T. *Mutat Res* 64(3): 195-204; 1979.

The micronucleus test has become a widely used screening procedure for the in vivo detection of chromosome breakage or loss induced in bone marrow erythroblasts by chemical mutagens. Little attention has been given to the statistical design of experiments employing this test. A sequential statistical analysis based on the negative binomial distribution is described. It permits the investigator to optimize the number of animals per test group and the number of cells analyzed per animal. The test will detect a predetermined increase in the incidence of micronucleated cells over that observed in the control population with chosen limits of probability of type I (α) and type II (β) error. In this case, α is the probability of declaring that a compound is mutagenic when it is not, and β is the probability of not declaring that a compound is mutagenic when, in fact, it is. The sequential test is slightly more powerful than a one-stage test based on the same distribution, and it would require less animals. An alternative sequential approach based on the binomial distribution is presented that is applicable when the number of cells analyzed per animal is variable. (10 refs)

- 79-4909 **Genes, Pollutants and Human Diseases.** (Eng) Trosko, J. E. (Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI 48824); Chang, C. C. *Q Rev Biophys* 11(4): 603-627; 1978.

Some of the basic concepts related to disease are examined using cancer as a model. The nature of carcinogenesis; the multistage nature of cancer and other chronic diseases; classes of genetic and environmental factors in carcinogenesis; chemical modification of the extent of DNA damage; chemicals that can modify DNA repair; chemical modification of the expression of genetic damage and its possible role in carcinogenesis; and genes, chemical pollutants, mutations, and evolution are discussed. Although attempts should be made to minimize human exposure to environmental pollutants which could induce mutations, it will never be possible to prevent mutations from occurring in some cells. Although initiating and promoting chemicals should be identified, it may be impossible to label a compound as dangerous or safe without considering the total context of the organism-chemical interaction. (116 refs)

- 79-4910 **Ribosome Accumulation and the Regulation of Epidermal Hyperplastic Growth.** (Eng) Argyris, T. S. (Dept. Pathology, SUNY Upstate Medical Center, Syracuse, NY 13210). *Life Sci* 24: 1137-1147; 1979.

The role of ribosomes in the regulation of epidermal hyperplastic growth (EHG) is reviewed. Ribosomes accumulate in large numbers during EHG, and their number returns to normal levels during the regression period, when the hyperplastic epidermis returns to its normal size. There is a rough correlation between the degree of EHG and the amount of ribosome accumulation in each epidermal cell. Elevated ribosome levels are also seen in chronic epidermal hyperplasia and in epidermal papillomas. It is suggested that the marked accumulation of ribosomes in epidermal cells, as well as other as yet unspecified linked molecular changes, produce an imbalance that keeps epidermal cells proliferating, resulting in hyperplastic growth. In epidermal tumors, this imbalance is locked in place, resulting in a permanent EHG condition. (31 refs)

- 79-4911 **Differences in Susceptibility to Herpes Simplex Virus Infection of Inbred Strains of Mice.** (Eng) Kirchner, H. (Inst. für Virusforschung, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Kochen, M.; Munk, K.; Hirt, H. M. *IARC Sci Publ* 24(11): 783-788; 1978.

Marked differences were observed between the susceptibility of adult C57BL/6 mice to infection with herpes simplex virus (HSV)-1. These differences were seen after various infection schedules but were most marked after ip infection. A significant difference between the LD₅₀ after ip infection was also observed between LPS(lipopolysaccharide)-resistant C3H/HeJ and the closely related LPS-sensitive C3HeB/FeJ mice. Injection of LPS significantly increased

the LD₅₀ after ip infection with HSV in C57BL/6 or C3H/HeJ mice but not in C3HeB/FeJ mice. In vitro pretreatment with LPS was necessary to demonstrate replication of HSV in mouse spleen-cell cultures. Such replication could be demonstrated in cultures of DBA/2 and C3HeB/FeJ but not in C57BL/6 or C3H/HeJ mice. (11 refs)

- 79-4912 Apudomas (First of Two Parts). (Spa) Varas Lorenzo, M. J. (Barcelona, Spain). *Rev Esp Enferm Apar Dig* 55(1): 89-98; 1979.

Literature on the embryological, endocrinological, and biochemical aspects of apudomas is reviewed. The apudomas were classified as orthoendocrine tumors, paraendocrine tumors, and multiple endocrine adenomatosis. (no refs)

- 79-4913 Histogenesis and Morphology of Colorectal Carcinoma. (Ger) Thurner, J. (Pathologisch-anatomisches Institut, Landeskrankenanstalten Salzburg, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria). *Wien Med Wochenschr* 129(10): 264-267; 1979.

The histogenetic and morphological aspects of colorectal carcinoma (CRC) are reviewed. At least half of all CRC's can be assumed to originate from neoplastic polyps. There is a clear relationship between the diameter of these polyps and the percentage of malignant transformation: 1% of all polyps measuring up to 10 mm in diameter are malignant, but >50% of the polyps >20 mm in diameter are malignant. About 70% of the neoplastic polyps are adenomatous polyps. Along with neoplastic polyps, certain intestinal polyposes (familial colonic polyposis, Gardner's syndrome, Turcot syndrome, and Peutz-Jeghers syndrome) and ulcerative colitis are considered the precursor stages of CRC. The majority of the CRC's are located in the rectum and sigmoid colon, and >80% are adenocarcinomas. The recent considerable increase in the incidence of CRC is attributed to exogenous causes such as increased fat consumption, which leads to increased secretion of coprostanol, coprostanone, bile acids, and total bile steroids and also to a change in the intestinal flora. There are racial but no geographic differences in incidence. The incidence is highest in the age bracket 60-70 yr. (25 refs)

- 79-4914 Origin and Dissemination of Human Urinary Bladder Carcinoma. (Eng) Weinstein, R. S. (Department of Pathology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL 60612). *Semin Oncol* 6(2): 149-156; 1979.

The origin and dissemination of human urinary bladder

carcinoma (BC) are reviewed. Human BC has an unpredictable course with respect to progression and recurrence, influenced perhaps by tumor-cell properties, host-tumor relationships, responses to therapy, and the coexistence of carcinoma in situ and solid bladder tumors in some patients. The clonality of human BC is uncertain, although evidence for monoclonal origin for most human tumors is accumulating. If human BC is monoclonal in origin, then multifocal lesions might be the result of dissemination of tumor cells in the bladder. Intra-epithelial dissemination may be an important feature of human BC, although it is not a certainty. Malignant cells may migrate laterally within the epithelium or may slough into the urinary space and be seeded onto bladder epithelium at secondary locations. In the latter case, procedures that may induce injury and/or proliferation of the epithelium (such as cystoscopy) are suspect as possible agents of dissemination or recurrence. Intra-epithelial dissemination of solitary tumor cells and nests of cells (Paget's disease) can be particularly conspicuous in bladders harboring extensive carcinoma in situ. The lateral expansion of sheets of malignant cells is well described in cases of carcinoma in situ. The development of metastases from carcinomas requires the completion of a sequence of seven events; prevention of early local invasion would be the most effective preventive measure since once the BC invades the stroma, the progression of the disease is usually rapid. Several theories to explain the mechanism by which tumors invade connective tissue are detailed: the mechanical theory (an expanding tumor forces its way into alternative locations), the cell-membrane alteration theory, the increased cell motility theory (particularly ameboidlike motility), the loss of cell polarity theory (cells become susceptible to chemotactic factors in novel ways), and the theory of breakdown of natural host barriers to invasion. The early stage of tumor invasion may prove to be a multifactorial process. (91 refs)

- 79-4915 On an Article by K. M. Pozharisskii Titled "Problems Concerning the Morphogenesis of Cancer of the Rectum and Large Intestine." (Rus) Gol'bert, Z. V. (No affiliation given). *Arkhl Patol* 41(3): 56-59; 1979.

Some principles formulated in a previous article on the morphogenesis of Cancer of the rectum and large intestine are critically reviewed. The author erroneously claimed that carcinoma in situ is the early stage of development of adenocarcinoma of the rectum and large intestine, but in fact Stages I, II, and III dysplasias precede carcinoma in situ. (no refs)

- 79-4916 Expression of Differentiated Functions in Hybrid Cells. (Eng) Klein, G. (Karolinska Institutet, Stockholm, Sweden). *Differentiation* 13(1): 61-62; 1979.

Data suggesting that certain chromosome segments carry genes that are critical to the neoplastic growth of given target cells are reviewed. The precise meaning of the nonrandom chromosomal changes occurring in neoplastic cells remains to be deciphered, taking into account the evidence that malignancy generally behaves as a recessive trait. (16 refs)

- 79-4917 Chromosomal Analysis of Exposed Populations: A Review of Industrial Problems. (Eng) Purchase, I. F. (Central Toxicology Lab., ICI Ltd., Alderley Park, Nr. Macclesfield, Cheshire, England). In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 258-267; 1978.

Although chemically induced mutational effects are theoretically possible in man, no definitive data are available for determining their practical significance. Most neoplasms are associated with chromosomal abnormalities; however, it is not known whether these abnormalities are primary or secondary phenomena and whether they are involved in the initiation of the neoplastic process or are merely associated with the progression of tumor growth. Factors which can influence the results of a study of an exposed population may be unrelated to the chemical itself; technical factors, age, viral infections, duration of exposure, smoking, and variations in the level of exposure should all be considered. It has been shown that there is a close association between the clastogenic effect and the carcinogenicity of a chemical, and that there is a dose-response relationship evident in some studies of chemical clastogens. Improved methods for the identification of chemical carcinogens, determination of the 'safe' dose of a carcinogen, and continued population monitoring are advised. Individual idiosyncracies must also be considered. More rapid techniques must be developed to estimate chromosomal damage with the same degree of accuracy as the classical technique. Another major challenge for the future will be in identifying confounding effects. Emphasis should be placed on the utility of studying abnormal aberration levels as a means of solving problems associated with potential and actual occupational carcinogenesis. (48 refs)

- 79-4918 Bacteria and Cancer. (Rus) Pozharisskii, K. M. (Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR). *Arkhl Patol* 41(4): 72-79; 1979.

Current literature on the role of bacteria in carcinogenesis is reviewed. Analysis of the incidence of spontaneous and carcinogen-induced tumors in germfree (GF) mice and their normal counterparts did not provide an unequivocal conclusion. There was no difference between GF and normal

NMRI/HAN mice in the frequency of lung tumors, but GF mice had a decreased frequency of mammary gland tumors and an increased frequency of tumors of the lymphoreticular system. The sc administration of methylcholanthrene induced fibrosarcomas in GF rats; dimethylbenz(a)anthracene sc induced adenocarcinomas of the mammary gland and myeloid leukemia. Epidemiological analyses have revealed a certain association between the incidence of cancer of the large intestine and the composition of the intestinal microflora. (81 refs)

- 79-4919 Alcohol as a Co-Factor in the Etiology of Cancer. (Eng) Schottenfeld, D. (Dept. Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021). *Cancer* 43(5, Suppl): 1962-1966; 1979.

Alcohol and tobacco appear to act synergistically in the pathogenesis of epithelial cancers of the oropharynx (excluding lip), larynx, and esophagus. For the subsites within the upper aerodigestive tract, over 10,000 deaths in United States men during 1978 may be attributed to tobacco and alcohol consumption. The cancer sites for which tobacco and alcohol are major determinants occur with greater frequency in men, blacks, lower socioeconomic groups, and with increasing urbanization and increasing age (35-70 yr). Because primary hepatocellular carcinoma occurs more commonly in patients with cirrhosis, chronic alcohol abuse is an important risk factor for carcinoma of the liver parenchyma. Although experimental animal studies have failed to demonstrate whether ethanol can independently initiate tumorigenesis, various alternative or associated biochemical and immunological mechanisms of action have been proposed to explain the effects of alcohol consumption on cancer incidence. (39 refs)

- 79-4920 Significance of Occupational Cancer. (Eng) Boyland, E. (London Sch. Hygiene and Tropical Medicine, London WC1, England). *Prog Biochem Pharmacol* 14: 76-81; 1978.

The significance of studies of occupational cancer is surveyed. At least 90% of human cancers are due to chemical agents, and about 80% are due to environmental factors. Many causes of human cancer have been found by investigation of occupational disease, and this approach is still the most promising. Because chemical carcinogens are difficult to identify by examination of human populations, it is essential to carry out animal tests on chemicals in the environment to obtain indications of carcinogenic activity. Chemical carcinogens can be divided into two groups: the first group (eg, alkylating agents) does not require metabolic transformation for activity; the second group (eg, nitrosamines and polycyclic hydrocarbons) requires metabolic or chemical activation. The metabolic reactions

REVIEW

involved in the activation of the second group are part of the normal detoxification processes. The first step in the activation of polycyclic aromatic hydrocarbons is the formation of epoxides or arene oxides. Their action is due to the presence of an ethylene group or double bond that can be activated and to their similarity in shape to constituents of the target DNA molecule. Vinyl chloride and trichloroethylene, two other carcinogens, combine with DNA in a manner similar to that of the arene oxides of the carcinogenic hydrocarbons. Occupational cancers have special significance because they can give indications of the specific causes of cancer, and recognition of causes of cancer in workers gives indications of the causes of cancer in the general population. (no refs)

- 79-4921 Fertility of the Diethylstilbestrol-exposed Offspring. (Eng) Siegler, A. M. (Dept. Obstetrics and Gynecology, State Univ. New York, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203); Wang, C. F.; Friberg, J. *Fertil Steril* 31(6): 601-607; 1979.

The effects of diethylstilbestrol (DES) on the subsequent fertility of women exposed to the drug in utero are reviewed. Many factors enter into the evaluation of patients with a documented DES exposure. In an ongoing study with 2,940 participants collated from four regional institutions, differences were found in accordance with modes of entrance into the study and geographic differences in patterns of drug exposure such as the median dose, duration, and onset of therapy. Preliminary results seem to suggest no statistical difference in the outcome of pregnancy in DES-exposed patients, compared with controls. Normal pregnancy and delivery can occur in the presence of vaginal and cervical DES-induced abnormalities. The effect on fertility and the outcome of pregnancy still must be evaluated, and even if an abnormality is found, no therapy is indicated unless it is shown that the abnormality is responsible for the reproductive dysfunction. Seminal abnormalities noted in DES-exposed men suggest that fertility may become impaired in some individuals. (40 refs)

- 79-4922 Survival Rates after Enucleation of Eyes with Malignant Melanoma. (Eng) Seigel, D. (Office Biometry and Epidemiology, Natl. Eye Inst., NIH, Bethesda, MD 20014); Myers, M.; Ferris, F.; Steinhorn, S. C. *Am J Ophthalmol* 87(6): 761-765; 1979.

Previously published data were pooled to determine whether enucleation of the eye in patients with primary melanoma of the uvea accelerates the dissemination of tumor cells, metastases, and mortality. Death rates for eye and skin melanoma and for cancer of the larynx, stomach, cervix, corpus, and breast, at selected stages of disease and treated by surgery, radiotherapy, chemotherapy, or a com-

bination of therapies, were analyzed. A pattern of high mortality rates in the early years following diagnosis and lower rates 6-10 yr thereafter was observed. It is suggested that the small number of patients available to follow-up is probably the cause for the previously reported increase in mortality 6-10 yr after enucleation for melanoma of the uvea. Enucleation often coincides with an active phase of malignancy, during which mortality increases, causing the high death rates in the years following diagnosis. An alternative explanation is given for the occurrence of metastases after surgery. Ocular tumors are often small at the time they become symptomatic or diagnosed. Metastases from such tumors to other areas of the body are likely to be even smaller and, consequently, may be difficult to diagnose at that time. This analysis of survival rates in patients with uveal melanoma and other cancers produced no evidence to alter the existing pattern of treatment for uveal melanoma. (4 refs)

- 79-4923 Cancer, Mathematical Models and Aflatoxin. (Eng) Carlborg, F. W. (Dept. Statistics, Univ. Chicago, Chicago, IL). *Food Cosmet Toxicol* 17(2): 159-166; 1979.

Four mathematical models (probit, logit, one-hit, and improved Mantel-Bryan) used to estimate the risk of low doses of carcinogens to humans were evaluated with respect to epidemiological and experimental data on aflatoxin carcinogenesis. In a study of the incidence of liver cancer in male rats fed various doses of aflatoxin, all four models fit the data about equally well. The calculated frequencies for the one-hit model matched the observed frequencies within the limits of statistical error. There were insufficient data to carry out this analysis for the probit or logit models. Best estimates of the relationship between aflatoxin dose and lifetime risk of liver cancer in rats, and the upper 99% confidence limits from the four mathematical models for the dose-response relationship between aflatoxin intake and risk of liver cancer in rats are presented. Besides the problem of choosing the most appropriate mathematical model, three other factors influence the results: species conversion, the choice of an end-point, and species selection. The estimated concentration of ingested aflatoxin for the US population was used with each model to calculate the corresponding annual number of liver cancers due to aflatoxin among US men. (18 refs)

- 79-4924 Excess Mortality of Men in France. Analysis of Medical Causes of Deaths. (Fre) Riondet, J. (No affiliation given). *Rev Prat* 29(22): 1819-1820; 1979.

The excess cancer mortality of French men over women in the age bracket 40-60 yr is significantly higher than that in the US and, especially, in Sweden. The mortality due to

tumors of the buccal cavity, pharynx, esophagus, and larynx is 5-17 times higher than that in Sweden and 4-5 times higher than that in the US. Alcohol and smoking are considered causes of the excess cancer mortality. (2 refs)

- 79-4925 Advances in Childhood Solid Tumors. (Eng) Sinks, L. F. (Div. Pediatric and Adolescent Oncology, Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Medical Center, Washington, DC); Sumer, T. *Adv Pediatr* 25: 415-450; 1978.

Advances in the therapy of solid tumors in children and adolescents are reviewed. The tumors discussed include Wilms' tumor, rhabdomyosarcoma, osteogenic sarcoma, Ewing's sarcoma, CNS tumors, neuroblastoma, retinoblastoma, malignant ovarian tumors, testicular tumors, and hepatoblastoma. (127 refs)

- 79-4926 Controversies in Nutrition. A Brief Review. (Eng) Arlin, M. (Univ. Alaska, Anchorage, AK). *Nurs Clin North Am* 14(2): 199-214; 1979.

The possible role of nutrition in a number of diseases, including cancer, is reviewed. The varied geographic distribution of different cancers (ie, the high incidence of gastric cancer in Japan and low incidence in the US and the high incidence of colon cancer in the US and low incidence in Japan) supports a nutritional role, particularly because groups migrating to countries of high cancer incidence tend to demonstrate an increased risk within the first generation. The possible role of high dietary fat, sugar, and protein intake in colon cancer is discussed together with the current belief in the protective effect of dietary fiber. (30 refs)

- 79-4927 Mechanism of Action of Diet as a Carcinogen. (Eng) Weisburger, J. H. (Naylor Dana Inst., Valhalla, NY 10595). *Cancer* 43(5, Suppl): 1987-1995; 1979.

The mechanism of action of diet as a carcinogen is reviewed. In the United States, stomach cancer has declined over the past 50 yr and it is beginning to decline in countries where the rate is still high. It is hypothesized that gastric cancer might stem from the formation in the stomach or in pickled foods of alkylnitrosourea compounds. Vitamins C and E may inhibit this process. The risk of gastric cancer might therefore be reduced by assuring consumption of vitamin C with all meals and by reducing dietary salt. Cancers of the colon, breast, and prostate are associated with high intake of dietary fat. The actual carcinogen responsible for these cancers might be an *o*-methylarylamine obtained during the frying of protein-

containing foods. Dietary fiber, vitamin C, and selenium have been implicated as protective elements in specific types of cancer, including cancer of the colon. Vitamin A and retinoids have been observed to reduce breast and bladder carcinogenesis. (61 refs)

- 79-4928 Dietary Habits and Cancer Epidemiology. (Eng) Wynder, E. L. (American Health Foundation, 320 E. 43rd Street, New York, NY 10017). *Cancer* 43(5, Suppl): 1955-1961; 1979.

The hypothesis that specific nutritional deficiencies and unbalanced metabolism from dietary excesses are important in the etiology of many of the most common human cancers is reviewed. Alcohol and nutritional deficiencies could enhance carcinogenesis in tobacco smokers by increasing the microsomal metabolic activation of specific tobacco carcinogens. It appears to be fat and/or cholesterol in the diet which is primarily responsible for the association between diet and colon cancer. Bile acid production appears to be particularly important in colon carcinogenesis, and stool bulk may be a negative modifying factor. The fact that Finns ingest large amounts of dietary fat but have low rates of colon cancer indicates that total fat alone is not the only factor in colon carcinogenesis, however. Breast cancer also appeared to be associated with dietary fat, particularly animal fat. High rates of postmenopausal cancers may be due to increased prolactin/estrogen ratios. (58 refs)

- 79-4929 Interaction of Drugs, Hormones, and Nutrition in the Causes of Cancer. (Eng) Lipsett, M. B. (Clinical Center, NIH, Bethesda, MD 20014). *Cancer* 43(5, Suppl): 1967-1981; 1979.

Hormones may act as promoters in the carcinogenic process, and occasionally their metabolites may act as antihormones or have new physiologic effects. Drugs can interact with the endocrine system in many ways. They can promote secretion of a hormone, alter its rate of removal from plasma, change plasma protein-binding characteristics, or modify routes of metabolism. Estrogens have a preparative effect on the uterine endometrium. There are biologic, clinical and epidemiologic reasons for believing that estrogen administration to postmenopausal women increases the risk of endometrial cancer. Although there are similar biologic reasons to associate prolonged estrogenic stimulation with breast cancer, evidence for such an association is weak. Oral contraceptive use has been associated with a variety of hepatocellular tumors. Although estrogens can effect several hepatic functions, it seems likely that the 17 α -alkyl and 17 α -ethinyl functions of the progestins and estrogens are involved in this process. The role of estrogen use during pregnancy in the causation of vaginal cancer in female offspring and the role of androgens in prostate cancer are discussed. (168 refs)

REVIEW

79-4930 Dietary and Nutritional Implications in the Multifactorial Etiology of Certain Prevalent Human Cancers. (Eng) Gori, G. B. (Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014). *Cancer* 43(5, Suppl): 2151-2161; 1979.

The role of diet in the etiology of human cancers is reviewed. It has been estimated that 60% of cancers in women and 40% of those in men are related to diet and nutrition. Evidence that diet, rather than other environmental or genetic factors, is involved in the causation of cancers such as those of the breast, colon, esophagus, and pancreas comes from animal studies and studies of migrant populations and homogeneous populations living and working in the same environments. The cancers that are highly correlated with diet show a great variation in incidence around the world and changes in rates with time. It is theorized that carcinogenesis is promoted by the metabolic derivatives of bile acids, protease enzymes, antioxidant deficiency, changes in an individual's hormone profile, excess or deficient nutrient and calorie consumption, and certain food-borne carcinogens. Protease inhibitors, a variety of natural and artificial dietary antioxidants, and fiber may inhibit the carcinogenic process. Chemical compounds occurring naturally in some foods appear to inhibit carcinogenesis by increasing the activity of the mixed-function oxidase system. Certain dietary components may also enhance or inhibit the absorption of carcinogens. (100 refs)

79-4931 Oral Contraceptives and Cancer Risk. (Swe) Gustafsson, J. A. (Dept. Chemistry, Karolinska Institutet, S-104 01 Stockholm, Sweden); Hagenfeldt, K. *Lakartidningen* 76(17): 1625-1627; 1979.

Epidemiological studies on the relationship between oral contraceptives (OC) and cancer risk are reviewed. The long-term use of OC for over 2 yr is believed to reduce the risk of benign breast tumors; the protective effect of OC against such tumors persists even after cessation of use. The data available do not show conclusively whether or not OC would modify the risk of breast cancer, but some data indicate that OC can increase the risk of breast cancer in certain groups of women (young women, women with benign breast tumors, and in women who used OC before their first pregnancy). There is an increased risk of endometrial cancer in women who used sequential OC, which have been withdrawn from circulation. The epidemiological studies indicate that OC can reduce the risk of ovarian cancer and that the long-term use of OC by predisposed women can increase the risk of cervical dysplasia and carcinoma in situ of the cervix, but there is no conclusive evidence on the effect of OC on the incidence of hypophyseal adenoma and malignant melanoma. OC cause a marked increase in the relative risk of hepatocellular adenoma after long-term use (over 3 yr); the risk increases with the steroid dose, the length of treatment,

and with the age of the patient. Diethylstilbestrol, used inadvertently during pregnancy, increases the risk of vaginal neoplasia in female offspring. (1 ref)

79-4932 Estrogens and Endometrial Cancer (2 Letters to Editor). (Eng) Horwitz, R. I. (Yale Univ. Sch. Medicine, New Haven, CT 06510); Feinstein, A. R.; Jick, H.; Watkins, R. N.; Rothman, K. J.; Walker, A. M. *N Engl J Med* 300(23): 1333-1334; 1979.

A recently published conclusion that estrogens are causally related to endometrial cancer was based on unverified evidence from an inadequately controlled study. The reported reversal of damage following discontinuation of estrogen use may reflect the fact that many uterine cancers are detected, if at all, only at necropsy. Estrogens induce bleeding as a side effect, which leads to the dilatation and curettage (D/C) that reveals these cancers. When estrogen is stopped, so is the bleeding and the use of D/C, so the cancer rates fall. The authors of the study respond that the accuracy of their data was verified, but they agree that discontinuation of estrogen use may only postpone the time of diagnosis. (12 refs)

79-4933 New Strategy in the Fight Against Cancer of the Female Genital Tract, Prompted by the Increasing Frequency of Endometrial Cancer. (Spa) de Arcos de la Plaza, M. (Seccion de Prevencion y Diagnostico Precoz del Cancer Genital Femenino, Seguridad Social, Zaragoza, Spain). *Acta Ginecol (Madr)* 33(10): 411-415; 1978.

The increasing incidence of endometrial cancer calls for the systematic cytological screening of selected high-risk groups. These include women with obesity, diabetes, hypertension, hirsutism, sterility, early menarche, late menopause, ovarian tumors, hyperplastic or polypoid lesions of the endometrium and/or endocervix, and menstrual disorders. (5 refs)

79-4934 Mind and Cancer (Letter to Editor). (Eng) Rosch, P. J. (American Inst. Stress, 124 Park Ave., Yonkers, NY 10703). *Lancet* 1(8129): 1302; 1979.

The importance of stress in the development of cancer has been suggested by the observation of an increased incidence of malignancy and of a prompt and impressive decline in immune function in persons who have lost their spouse. In addition, the patient's state of mind is important in the fight against cancer, and patients should be offered an opportunity to participate actively in their own recovery. (7 refs)

- 79-4935 Inositol Phospholipids in Membrane Function. (Eng) Michell, R. H. (Dept. Biochemistry, Univ. Birmingham, P.O. Box 363, Birmingham B15 2TT, England). *Trends Biochem Sci* 4(6): 128-131; 1979.

The role of inositol phospholipids [phosphatidylinositol (PI), phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate] in membrane function is reviewed. Inositol lipids appear to be intimately involved in Ca^{2+} -mediated control of cell functions by hormones and other ligands, in cell proliferation, and in the attachment of enzymes to the plasma membrane. A PI response (stimulation of PI metabolism) can be provoked in any type of cell, provided that it possesses appropriate receptors. Many or all of the receptors that stimulate PI metabolism are similar: their action on target cells involves Ca^{2+} in some essential way, and they elevate cellular cyclic guanosine monophosphate concentrations. Activation of these receptors increases the cytosol Ca^{2+} concentration (CCC), which brings about other responses. The PI response frequently and, perhaps, universally accompanies the action of any receptor whose activation increases the CCC, and it is independent of the CCC. Fluctuations in CCC can exert appreciable control over the progression of cells through the cell cycle, with mild elevation of the CCC at appropriate times tending to accelerate proliferation. There is evidence of an increase in the rate of PI turnover in the proliferating state compared with quiescent cells of the same type; other lipids are usually unaffected. There may be a close correlation between mobilization of Ca^{2+} through the plasma membrane and an increased rate of PI turnover, without direct evidence as to whether the two events are causally related. The observation that alkaline phosphatase was released from slices of liver if they were incubated with a PI-specific phospholipase C isolated from a bacterial culture filtrate was recently confirmed. Some other plasma membrane ectoenzymes were released from liver and RBC membranes by the same treatment. PI is undoubtedly implicated in some specific and essential way in the normal attachment of these enzymes to the external surfaces of cell plasma membranes. (37 refs)

- 79-4936 Differentiation and Cancer. (Eng) Cairns, J. (Imperial Cancer Res. Fund, Mill Hill Labs., London, England). *Differentiation* 13(1): 67; 1979.

The conversion of a cell into a cancer cell can be thought of as an alteration in its state of differentiation, and mechanisms that may be involved in this process are discussed. Most human cancers arise in epithelial stem cells. These cancers are probably a change in phenotype due to a combination of mutation and altered pattern of regulation of gene expression. It seems likely that each particular class of cancer is the result of a particular alteration in the pattern of gene expression, rather than the expression of a cancer gene common to all cancers, making it unlikely that there is a universal cure for cancer. (no refs)

- 79-4937 The Significance of Cyclic AMP and Cyclic GMP in Cancer Treatment. (Eng) Tisdale, M. J. (Dept. Biochemistry, St. Thomas's Hosp. Medical Sch., London SE1 7EH, England). *Cancer Treat Rev* 6(1): 1-15; 1979.

The significance of cyclic AMP (cAMP) and cyclic GMP (cGMP) in cancer therapy is reviewed. Various chemical carcinogens and tumor promoting agents cause increases or decreases in the basal level of cAMP and alterations in the hormone responsiveness of their target tissues. Oncogenic viruses tend to cause a decrease in cAMP after transformation. A number of carcinogens have also been shown to stimulate or inhibit guanylate cyclase. Transformation tends to reduce adenylate cyclase activity; these early alterations reflected in more stable changes in enzyme activity in the resultant tumors. There are widely different levels of cyclic nucleotides in tumor cells. The apparent functional deficiency of cAMP in some tumors may be brought about by a disproportionate increase in the level of cGMP. cAMP may potentiate tumor development by inhibition of a DNA repair process. cGMP may also promote cell growth and transformation. There is evidence to indicate that cAMP can act as a tumor growth inhibitor in certain systems. In some systems, cyclic nucleotides may be involved in the regulation of tumor cell differentiation and maturation. If the activity or pattern of phosphodiesterases in neoplastic cells differs from those of normal cells, it may be possible to design drugs that will specifically inhibit the phosphodiesterase activity of only those cells and thereby increase the intracellular concentration of cAMP in cancer cells. (166 refs)

- 79-4938 Proliferation of Hepatocytes. (Eng) Leffert, H. L. (Cell Biology Lab., Salk Inst. Biological Studies, San Diego, CA); Koch, K. S. *Ciba Found Symp* 55: 61-94; 1978.

Factors that control the proliferation of liver cells in vitro and the manner in which agents that cause liver cancer alter growth controls are reviewed. Hepatocyte proliferation may be controlled by reversible patterns of endocrine changes, monitored by the liver, involving known hormones and their receptors. A two-program model of related interactions among nutrients, specific lipoproteins, and highly phosphorylated nucleotides is postulated. This hypothesis is derived from in vitro studies of rat hepatocyte proliferation under chemically defined conditions and from in vivo studies with partially hepatectomized, hormone-infused, developing and lipotrope-deficient rats. Liver proliferative states appear to be correlated with defined patterns of endocrine changes. The physiochemical basis of these patterns is in part a set of chemical equilibria between regulatory signals and their hepatocyte receptors; the pattern itself or a subset of its elements may determine specificity. Hepatocarcinogenesis may involve altered normal responsiveness as a concomitant and/or as a cause of

REVIEW

chemically induced transformation. Promising in vitro approaches for studies of chemical hepatocarcinogenesis are outlined. (34 refs)

79-4939 The Association of Pregnancy and Breast Cancer. (Eng) Zinns, J. S. (Dept. Surgery, New York Medical Coll., Metropolitan Medical Center, New York, NY). *J Reprod Med* 22(6): 297-301; 1979.

The association of pregnancy and breast cancer (BC) is reviewed. The incidence of BC during pregnancy is rare; incidences of 3/10,000 and 10/62,000 pregnancies have been found in the literature. The av age of patients afflicted with BC while pregnant is 35-36. The quick progress of the disease during pregnancy may be due to increased hor-

monal stimulation, which causes major alterations in breast physiology. There is an increase in vascularity and lymphatic permeability. The altered immune response during pregnancy also influences the prognosis to some degree. The av delay in seeking medical attention is 11 mo for pregnant or lactating patients, in contrast to 4 mo for nonpregnant patients. The histological distribution of BC in pregnant women is similar to that in nonpregnant women. Careful and frequent examination of the breast during pregnancy is recommended. Biopsies of three dimensional lumps should be performed, and low-dose mammography with appropriate abdominal shielding is a safe diagnostic method during pregnancy. Reports indicate that there has been continued improved survival, especially for early disease. In a series of 88 patients, a 90% 5-yr survival rate was reported for those with Stage I disease. (42 refs)

CHEMICAL CARCINOGENESIS

- 79-4940 Non-activation in the Ames Test (Letter to Editor). (Eng) Hope, J. (Environmental Safety Div., Unilever Res. Lab., Colworth House, Sharnbrook, Bedford, England). *Mutat Res* 67(2): 197-198; 1979.

The previous suggestion that in the *Salmonella typhimurium* test, a nonactivation 'control' consisting of incubation of the chemical at the highest dose level with the S9 preparation, but without the NADPH-generating system, is discussed. False negatives may be obtained when nonactivation systems that include S9 preparations are used. (no refs)

- 79-4941 In Utero Sister Chromatid Exchange Analysis for Detection of Transplacental Mutagens. (Eng) Kram, D. (Section Cellular Aging and Genetics, Lab. Cellular and Molecular Biology, Gerontology Res. Center, Natl. Inst. Aging, NIH, Baltimore, MD 21224); Bynum, G. D.; Senula, G. C.; Schneider, E. L. *Nature* 279(5713): 531; 1979.

A new approach for the detection of fetal DNA damage through the enumeration of sister-chromatid exchanges (SCE's) in mouse fetal chromosomes is described. In utero SCE analysis is relatively simple, rapid, and reproducible, and it requires small numbers of animals, allows simultaneous examination of the effect of agents on fetal and maternal cells, and may be more sensitive than previously described techniques. (16 refs)

- 79-4942 Milky Spots (*Taches Laiteuses*) as Structures Which Trap Asbestos in Mesothelial Layers and Their Significance in the Pathogenesis of Mesothelial Neoplasia. (Eng) Kanazawa, K. (Dept. Surgery, Univ. Tsukuba Sch. Medicine, Sakura-Mura, Niihari-Gun, Ibaraki, 300-31, Japan); Roe, F. J.; Yamamoto, T. *Int J Cancer* 23(6): 858-865; 1979.

The structure and function of milky spots (*Taches laiteuses*) in the mesothelial layer of mice are described, along with the sequential changes that occur in these spots after exposure of the mice to asbestos. Crocidolite asbestos was injected sc (2 doses of 30 mg in 0.4 ml saline on 2 successive days) into the flanks of CBA/lac mice. Asbestos fibers were found in mediastinal milky spots >442 days after the injection, in the form of either naked fibers or asbestos bodies. Milky spots were the only structure in which asbestos fibers were observed in the mesothelial layer. The fact that asbestos fibers were found in the liver, spleen, kidney, and brain, in addition to the milky spots, suggests that they were transported by the bloodstream throughout the body. This assumption was confirmed by

the similar distribution of asbestos after iv administration. The vascular and cellular structure of the milky spots is such that they are particularly likely to trap blood-borne asbestos fibers. Hyperplastic changes were observed in milky spots after both sc and iv administration of asbestos. Milky spots may be involved in the genesis of mesothelial tumors in animals following their exposure to asbestos. (30 refs)

- 79-4943 Enhancement by Asbestos of Oncogenesis by Moloney Murine Sarcoma Virus in CBA Mice. (Eng) Kanazawa, K. (Dept. Surgery, Univ. Tsukuba Sch. Medicine, Sakura-Mura, Niihari-Gun, Ibaraki 300-31, Japan); Yamamoto, T.; Yuasa, Y. *Int J Cancer* 23(6): 866-874; 1979.

The enhancement of Moloney murine sarcoma virus-induced tumorigenesis by trace quantities of asbestos was studied in 3-wk-old CBA mice. Sixty-one mice were inoculated ip with 5 µg of finely ground crocidolite asbestos and 10⁵ focus-forming units of the virus. Forty-four of the mice developed palpable ip tumors, half of which died from their tumors within 100 days. The same amount of quartz and carbon similarly administered gave lower tumor incidences, 19.4% (3.2% fatal) and 11.9% (1.5% fatal), respectively. Only 1/59 mice inoculated with the virus alone developed a palpable ip tumor, and this tumor regressed spontaneously within 10 days. No tumors were encountered in mice treated with asbestos, quartz, or carbon alone. All the neoplasms had the appearance, under the light microscope, of anaplastic sarcomas. Most of them were confined to the serosal surface of the abdominal cavity, although invasion of underlying tissues was observed in some of the animals that died. Electron microscope examination of the tumors revealed the presence of C-type particles budding from the cellular surface. Some neoplastic cells showed the characteristic features of mesothelial lining cells. The role of milky spots (*Taches laiteuses*) in oncogenesis induced by asbestos and virus, especially in the induction of mesothelioma, is discussed. (35 refs)

- 79-4944 Heavy Metal (Cd, Zn, Pb, Cu, Cr) Content in Cigarette Brands Commonly Smoked in West Germany. (Ger) Muller, G. (Institut für Sedimentforschung, Universität Heidelberg, Im Neuenheimer Feld 236, D-6900 Heidelberg, W. Germany). *Chemiker-Zeitung* 103(4): 133-137; 1979.

The tobacco in 15 commercial cigarette brands commonly smoked in West Germany were analyzed for heavy metal levels by atomic absorption spectrometry. The following

minimum, mean, and maximum concentrations (in $\mu\text{g/g}$ = ppm) were found: Cd: 1.07, 1.46, 2.30; Zn: 33, 45, 64; Pb: 2.4, 3.3, 4.3; Cu: 10, 21.7, 34; Cr: 3.4, 4.9, 6.7; Fe: 292, 428, 572; Mn: 71, 133, 176. The high Cd level, which is due to uptake from emissions rather than from the soil, is emphasized with respect to a potential cocarcinogenic effect with the polycyclic aromatic hydrocarbons present in cigarette smoke. Literature data show that Cd has carcinogenic and teratogenic effects only upon parenteral administration. At an estimated transfer rate of 10%, the Cd uptake amounts to 0.08-0.37 $\mu\text{g/cigarette}$. (23 refs)

- 79-4945 Primary Biochemical Defect in Copper Metabolism in Mice with a Recessive X-Linked Mutation Analogous to Menkes' Disease in Man. (Eng) Prins, H. W. (Interuniversity Reactor Inst., Delft, Netherlands); Van den Hamer, C. J. *J Inorg Biochem* 10(1): 19-27; 1979.

Copper metabolism was studied in Brindled mice of three phenotypes: normal mice, mice with an X-linked defect comparable to Menkes' disease in man (MD mice), and heterozygous mice. ^{64}Cu or ^{67}Cu was administered ip or po. The copper concentrations were elevated in the kidneys, mucosa and muscle of the gastrointestinal tract, pancreas, and bones of the heterozygous adults compared with the normal adults; there was no significant difference in the liver concentrations. The distribution of ^{67}Cu in young heterozygous and MD mice after po administration was abnormal relative to normal mice. The kidneys of both heterozygous and MD mice irreversibly stored ^{64}Cu as a cytoplasmic protein with a mol wt of 10,000 daltons. This particular protein fraction also contained a larger amount of stable copper. There are three models that could explain the accumulation of the 10,000-dalton protein of the kidney: irreversible copper binding in an abnormal species of the protein (fraction I); a block in the copper transport from fraction I to fraction II, or an inability of copper to bind to fraction II. In the livers of both heterozygous and MD mice, more ^{64}Cu was bound in fraction II and less in fraction I than in normal mouse liver. (9 refs)

- 79-4946 On the Problems of Evaluating Bronchial Carcinoma After Exposure to Chromium Compounds. (Ger) Zober, A. (Institut für Arbeits- und Sozialmedizin und Poliklinik für Berufskrankheiten, Universität Erlangen-Nürnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany). *Int Arch Occup Environ Health* 43(2): 107-121; 1979.

Twenty-seven cases of lung disease due to occupational exposure to hexavalent chromium (Cr VI, 24 cases) and trivalent chromium (Cr III, 3 cases) at 7 industrial plants are reported. Lung cancer was diagnosed in 17 patients, 3

of whom had been exposed to Cr III; lung disease without carcinoma (bronchitis, emphysema, and fibrosis) was seen in 10 patients. The lung cancer was acknowledged as occupational disease in 14 cases; these 14 patients had been exposed for 2-32 yr, and the latent period (length of exposure plus delay after cessation of exposure) was 10-53 yr. The lung cancer was always preceded by emphysema or chronic bronchitis. The chromate content was analyzed in the lung tumor and in the normal lung tissue in 3 cases; the Cr content was higher in the cancer tissue than in the normal tissue in 2 cases, and it was higher in the normal tissue in 1. Histological data available for 10 cases showed squamous epithelial carcinoma in 8, dedifferentiated adenocarcinoma in 1, and small-cell carcinoma in 1; the squamous epithelial carcinoma was associated with large-cell carcinoma in 1 patient. There were no marked differences between the cancer patients and the 10 other patients with non-neoplastic lung diseases in the length of exposure and latency. (27 refs)

- 79-4947 Experimental Respiratory Carcinogenesis in Hamsters: Environmental, Physicochemical and Biological Aspects. (Eng) Stenback, F. (Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE 68105); Rowland, J. *Oncology* 36(2): 63-71; 1979.

The potential hazards associated with silicone dioxide (SiO_2), manganese dioxide (MnO_2), and agar gelatin (gel) in combination with benzo(a)pyrene (BP), dibenz(a,j)acridine (DBA), and the carrier dust Fe_2O_3 were evaluated following intratracheal administration to Syrian golden hamsters. Survival times among treated hamsters were lower than those among controls, but respiratory tract tumors developed only in animals given DBA or BP plus dust or gel. BP alone induced respiratory neoplasms in 5/46 hamsters; BP plus SiO_2 induced such tumors in 21/48 animals; and BP plus MnO_2 or 0.5% gel induced tumors in 6/46 and 6/47 animals, respectively. DBA plus Fe_2O_3 induced a respiratory neoplasm in 1/45 animals. Particle size was correlated with retention rate but not with carcinogenicity. The respiratory tumors induced by BP plus SiO_2 were preceded by proliferative dysplastic alterations not seen in animals treated with BP and MnO_2 or DBA and Fe_2O_3 . It is concluded that extensive preneoplastic changes are associated with subsequent tumor formation and are not due only to treatment with certain hydrocarbon-dust combinations. (36 refs)

- 79-4948 Histopathological Changes in Nasal Mucosa of Workers at Norwegian Nickel Refinery. (Eng) Solberg, L. A. (Dept. Pathology, Ulleval Hosp., Oslo, Norway); Torjussen, W. *Acta Otolaryngol [Suppl] (Stockh)* 360: 124; 1979.

Histopathologic changes in the nasal mucosa of 318 nickel workers at a Norwegian refinery, 15 retired nickel workers,

and 57 age-matched controls were studied. Nasal carcinoma was found in 2 nickel workers (0.6%), and epithelial dysplasia was found in 12% of the workers, 47% of the retired workers, and one control (a 65-yr-old carpenter). The data suggest that nickel compounds or factors associated with nickel refinery work may be involved in the causation of nasal carcinoma and epithelial dysplasia. (2 refs)

- 79-4949 Platinum Tetrachloride: Mutagenicity and Methylation with Methylcobalamin. (Eng) Taylor, R. T. (Biomedical Sciences Div., Lawrence Livermore Lab., Univ. California, Livermore, CA 94550); Happe, J. A.; Hanna, M. L.; Wu, R. *J Environ Sci Health [A]* 14(2): 87-109; 1979.

The methylation and mutagenicity of platinum tetrachloride (PtCl_4) for two closely related Chinese hamster ovary cell lines (CHO-S and CHO-AUXB1) were studied. Micromolar concentrations of PtCl_4 and methylcobalamin (MeB-12) reacted in water. The demethylation of MeB-12 was 90% complete after 24 hr, but the rate could be increased by catalytic amounts of K_2PtCl_6 . Pt products isolated by column chromatography included MePtCl_3^- as the principal product and $\text{MePt}(\text{H}_2\text{O})\text{Cl}_2^-$, which was identified by nuclear magnetic resonance data. In CHO-S cells, PtCl_4 induced forward mutations to the 8-azaguanine resistance/hypoxanthine-guanine phosphoribosyl transferase locus, but not to ouabain resistance. It also induced the reversion of CHO-AUXB1, a multiple auxotroph. The mutagenic effects of PtCl_4 for both cell lines were dose-dependent in the range of 5-30 μM . (18 refs)

- 79-4950 The Effect of Various Selenium Compounds in the Development of Ehrlich Ascites Tumor Cells (Meeting Abstract). (Eng) Greeder, G. (Univ. Illinois, Urbana, IL 61801); Milner, J. A. *J Nutr* 109(6): 32; 1979 (no refs)

- 79-4951 Dietary Supplementation of Stable Strontium (Meeting Abstract). (Eng) Skoryna, S. C. (St. Mary's Hosp. Centre, Montreal, Canada); Inoue, S.; Fuska, M. *J Nutr* 109(6): 33; 1979 (no refs)

- 79-4952 Potentiating Effect of Methyl Methane Sulfonate on Friend Virus Leukemogenesis In Vivo. (Eng) Raikow, R. B. (Cancer Res. Unit, Clinical Radiation Therapy Res. Center, Allegheny General Hosp., Pittsburgh, PA 15212); Meredith, R. F.; Brozovich, B. J.; Seeman, P. R.; Livingston, A. E.; Okunewick, J. P. *Proc Soc Exp Biol Med* 161(2): 210-215; 1979.

Studies were conducted to determine if methyl methanesulfonate (MMS) would act as a potentiating agent for an RNA cancer virus in vivo. MMS (2 mg ip) given 5 hr before friend leukemia virus (FLV) injection enhanced the leukemogenic action of FLV in virus-sensitive SJL/J mice and also in relatively virus-resistant B10SJF₁ mice. MMS also decreased the humoral immune response, as measured by a plaque-forming-cell assay. However, the timing of the effect of MMS on the immune system did not coincide with the timing of the MMS-related potentiation of leukemia. Hence, it is suggested that the potentiating effect of this chemical on viral leukemogenesis is more likely due to events occurring at the intracellular level rather than at the level of the humoral immune response. (35 refs)

- 79-4953 Cross Sensitivity of Mutator Strains to Physical and Chemical Mutagens. (Eng) Nasim, A. (Div. Biological Sciences, Natl. Res. Council Canada, Ottawa, Ontario K1A 0R6, Canada); Brychey, T. *Can J Genet Cytol* 21(1): 129-137; 1979.

Ten different mutator strains of *Saccharomyces cerevisiae* were tested for cross sensitivity to two alkylating agents, ethyl methanesulfonate (EMS) and methyl methanesulfonate (MMS), to determine if any were defective in the repair systems which normally deal with damage caused by these agents. For one of the mutators, strain *mut2-1*, it was shown by genetic analysis that mutator activity and MMS sensitivity are both controlled by the same gene. Two mutants, *mut2-1* and *mut7-1*, were found to be sensitive to MMS but normal in reaction to ultraviolet and γ -rays. Another group is represented by *mut1*, *mut6* and *mut8* which are not sensitive to any of the mutagens tested so far. Mutator strain *mut2-1* was also shown to be not significantly altered for levels of UV-induced forward and reverse mutations. These observations lend support to the idea of multiple repair systems that deal with DNA damage caused by different agents and also show that mutator activity can often result from the loss of normal cellular repair systems. (35 refs)

- 79-4954 Silver Sulfadiazine: Lack of Mutagenic Activity. (Eng) McCoy, E. C. (Dept. Microbiology, New York Medical Coll., Valhalla, NY 10595); Rosenkranz, H. S. *Chemotherapy* 24(2): 87-91; 1978.

Silver sulfadiazine, an antimicrobial agent, was non-mutagenic toward *Salmonella typhimurium* strains TA1535, TA1537, TA1538, and TA100 in the presence and absence of a microsomal activation mixture. In view of the relationship between mutagenicity in this system and carcinogenicity in animals, the findings suggest that the compound is also devoid of carcinogenic properties. (30 refs)

- 79-4955 Enhanced Colonic Carcinogenesis with Azoxymethane in Rats after Pancreaticobiliary Diversion to Mid Small Bowel. (Eng) Williamson, R. C. (Surgical Services, Shriners Burns Inst., Boston, MA); Bauer, F. L.; Ross, J. S.; Watkins, J. B.; Malt, R. A. *Gastroenterology* 76(6): 1386-1392; 1979.

To examine the role of biliary secretion in the differential production of chemically induced enteric neoplasia, pancreaticobiliary diversion (PBD) was performed on male Fischer rats before or after treatment with azoxymethane (AOM, 10 mg/kg/wk, sc, for 16 wk). The procedure involved diverting pancreaticobiliary secretion from the duodenum to the mid-small bowel. RNA and DNA levels in the jejunal mucosa were unchanged 30 wk after PBD. However, in the upper ileum of rats given AOM or vehicle, PBD increased the levels of both nucleic acids by 37%-102%. At 30 wk, PBD increased the RNA content of the right colon in vehicle-treated rats by 29% and the DNA content of both the right and left colon of AOM-treated rats by 30%-31%. AOM alone increased the RNA content of the jejunum and upper ileum by 31% and 17%, respectively. Neither AOM nor PBD influenced the fecal excretion of bile acids. PBD preceding AOM increased the number of tumors throughout the small bowel. Papillary or tubular adenocarcinomas (68% of the total) predominated in the duodenum and mucinous adenocarcinomas (23% of the total) predominated in the jejunum and ileum. In the large bowel, PBD increased the incidence of colonic tumors from 1.26 to 3.16 per rat ($p < 0.005$) when it preceded AOM and from 1.26 to 2.70 per rat ($p < 0.02$) when it followed AOM. Tumor frequency was greatest in the distal colon, and adenocarcinomas predominated. The incidence of metastatic adenocarcinomas increased when PBD preceded AOM. The potentiation of colonic neoplasms by PBD probably depends on the stimulation of colonic mucosal proliferation. (45 refs)

- 79-4956 The Effect of Prolonged Ethanol Intake on Some Carcinogen-activating Enzymes in Mice. (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Dorrel, H. M.; Jenner, M.; Pinnock, M. H.; Williams, D. C. *Biochem Pharmacol* 28(7): 1139-1141; 1979.

The effect of prolonged intake of subchronic and chronic levels of ethanol on the hepatic microsomes of male albino TO mice was investigated, along with changes in some of the parameters associated with carcinogen activation. Cytochrome P-450 and aryl hydrocarbon hydroxylase levels were increased in mice that received 1% or 10% (volume/volume) absolute ethanol in their drinking water for 24 or 32 wk. These increases corresponded to a consistent rise in microsomal protein values throughout the experiment. The binding of benzo(a)pyrene to DNA was significantly increased during 1% ethanol treatment, but it

returned to the control level after 20 wk. In mice receiving 10% ethanol, the binding of benzo(a)pyrene was consistently decreased, returning to the control level only after 32 wk. This study demonstrated that an enzyme involved in carcinogen activation can be increased as a result of the adaptation of the hepatic microsomal ethanol-oxidizing system to prolonged ethanol ingestion. (28 refs)

- 79-4957 Research Contributions: Mutagenic Activity of Ethylene Oxide, Ethylene Glycol, and 2-Chloroethanol Residues in Plastic Materials Sterilized with Ethylene Oxide. (Fre) Conan, L. (Laboratoire d'Histopathologie Certi, 59 avenue de Paris, 78000 Versailles, France); Foucault, B.; Siou, G.; Chaigneau, M.; Le Moan, G. *Ann Falsif Expert Chim* 72(773): 141-151; 1979.

The mutagenicity of ethylene oxide (EO) in aqueous solution or on ip implanted polyethylene or polyvinyl chloride sterilized with EO, of ethylene glycol (EG), and 2-chloroethanol (CE) was studied in male Swiss C.F.L.P. mice. The presence of chromosome aberrations in bone marrow cells and the percentage of polychromatic erythrocytes carrying Howell-Jolly bodies were used as indicators of mutagenicity. The quantity of EO introduced with the sterilized plastics was 0.5-5 mg/animal; the animals were sacrificed 30-50 hr after implantation. EO was also administered ip (1-200 mg/kg) and iv (100 mg/kg); EG was administered ip (1.25 and 6.25 ml/kg) and po (2.5-12.5 ml/kg); and CE was administered po (0.025-0.1 ml/kg) and ip (0.01 and 0.05 ml/kg). Untreated animals served as controls. The plastics sterilized with EO as well as CE failed to produce any signs of mutagenic activity, but EO and EG caused an increase in the percentage of erythrocytes with Howell-Jolly bodies from 0.23% in the controls to 0.13-0.47% and 0.18-0.51%, respectively. Chromosome aberrations were not seen. (23 refs)

- 79-4958 Ethanol Inhibition of Vinyl Chloride Metabolism in Isolated Rat Hepatocytes. (Eng) Hultmark, D. (Dept. Microbiology, Univ. Stockholm, S-106 91 Stockholm, Sweden); Sundh, K.; Johansson, L.; Arrhenius, E. *Chem Biol Interact* 25(1): 1-6; 1979.

Factors which could influence the metabolism of vinyl chloride (VC) by the liver were studied using hepatocytes and liver microsomes from untreated and phenobarbital (PB)-pretreated male strain R Wistar rats. VC incubated with hepatocytes was metabolized as a linear function of time. The metabolism was unaffected by PB pretreatment or metyrapone (40 μ M), but was strongly inhibited by ethanol (4 mM) and tetrahydrofuran. Dichloro-p-nitroanisole O-demethylase was strongly stimulated in the hepatocyte preparations by PB pretreatment, and the metabolism of dichloro-p-nitroanisole was partially inhibited by metyrapone, especially after PB pretreatment.

The liver microsomes showed a high capacity to convert VC to non-volatile products, this capacity being dependent on the presence of a NADPH-generating system. The microsomes were even more sensitive than the intact hepatocytes to ethanol inhibition. (20 refs)

- 79-4959 Mutagenicity of Vinyl Chloride, Vinylidene Chloride and Chloroprene in V79 Chinese Hamster Cells. (Eng) Drevon, C. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Kuroki, T. *Mutat Res* 67(2): 173-182; 1979.

The mutagenicity of vinyl chloride (VC), vinylidene chloride (1,1-dichloroethylene: VDC) and chloroprene (2-chloro-1,3-butadiene) was tested in V79 Chinese hamster cells in the presence of a 15,000 x g liver supernatant from phenobarbital-pretreated rats and mice. Mutations in terms of 8-azaguanine and ouabain resistance were induced in a dose-related fashion by exposure to VC vapor in the presence of the liver supernatant from phenobarbital-pretreated BDVI rats. VDC and chloroprene vapors induced a dose-related toxicity when tested with the rat liver supernatant, but these two compounds were not mutagenic in V79 cells under the assay conditions. The results are discussed with regard to the metabolic activation of the compounds and to the correlation between the carcinogenicity of VC in humans and experimental animals. (31 refs)

- 79-4960 Toxicity of Low Concentration Long-Term Exposure to an Airborne Mixture of Nitrous Oxide and Halothane. (Eng) Coate, W. B. (Hazleton Labs. America, Vienna, VA); Kapp, R. W.; Ulland, B. M. *J Environ Pathol Toxicol* 2(5, Special): 209-231; 1979.

To determine the reproductive, teratologic, cytogenetic, and tumorigenic effects of long-term exposures to escape levels of halothane + nitrous oxide, male and female Sprague-Dawley and Fischer rats were exposed to air, to 1 ppm halothane + 50 ppm N₂O, or to 10 ppm halothane + 500 ppm N₂O for 7 hr/day, 5 days/wk, for appropriate periods of time. In one experiment, young adult female rats were exposed for 60 days, then mated and reexposed from gestation day 1 or 6 to day 15. The former were permitted to deliver naturally, and the latter were delivered by C-section on day 20. The young adult males used in breeding were also exposed for 60 days prior to mating and then for a total of 52 wk thereafter. At termination, bone marrow cell and spermatogonial metaphase preparations were made and assessed for cytogenetic abnormalities. The mated females were evaluated for ovulation, pre- and postimplantation loss, fetal growth, fetal abnormalities, and early postnatal development. In a parallel experiment, 50 male and 50 female weanling rats in each group were ex-

posed for 104 wk to the same levels and then evaluated for tumor development, with emphasis on the reticuloendothelial system. There was a significant reduction in ovulation and implantation efficiency from exposure to the higher levels and a slightly retarded fetal development at both levels. No teratologic or abortifacient effects were noted. No tumorigenic effects were observed. However, cytogenetic damage to both bone marrow and spermatogonial cells was seen at both levels. (19 refs)

- 79-4961 Report on Carcinogenesis Bioassay of 1,2-Dichloroethane (EDC). (Eng) Anonymous (U.S. Dept. Health, Education, and Welfare, NCI, NIH, Bethesda, MD 20014). *Clin Toxicol* 14(2): 225-230; 1979.

The carcinogenicity of 1,2-dichloroethane (EDC, 47-299 mg/kg/day, 5 days/wk for 78 wk, po) for Osborne-Mendel rats and B6C3F1 mice was studied. In male rats, EDC caused forestomach cancers, hemangiosarcomas of multiple organs, and sc fibromas. Female rats given EDC developed mammary cancers; in some animals given the highest dose of EDC (95 mg/kg/day) these tumors appeared after as little as 20 wk. The chemical also caused breast cancers and uterine cancers in female mice and respiratory tract cancers in male and female mice. (no refs)

- 79-4962 Vinylidene Fluoride: Metabolism and Induction of Preneoplastic Hepatic Foci in Relation to Vinyl Chloride. (Eng) Stockle, G. (Institut für Toxikologie, Universität Tübingen, Wilhelmstrasse 56, D-7400 Tübingen-1, W. Germany); Laib, R. J.; Filser, J. G.; Bolt, H. M. *Toxicol Lett* 3(6): 337-342; 1979.

The tumorigenicity and metabolism of vinyl chloride (VC) and vinylidene fluoride (VF) were compared in Wistar rats. Exposure of newborn rats to VC (2,000 ppm, 8 hr/day, 5 days/wk) for 4 wk resulted in the formation of ATPase-deficient hepatocellular foci. Similar exposure to VF produced a few single foci after 10 wk. After 14 wk of exposure to VF, the number of foci was less than that observed after 4 wk of exposure to VC, and it was about one 1/100 the number found after 10 wk of exposure to VC. The rate of the metabolic conversion of VF in the rat was found to be 2 orders of magnitude lower than that of VC. The very slow metabolism of VF may explain why this compound is much weaker in eliciting preneoplastic hepatic foci in newborn rats than VC. (21 refs)

- 79-4963 Effect of DDT on Urinary Excretion of Mutagenic Metabolites of 2-Acetylaminofluorene (2-AAF) in Rats in Acute and Chronic Experiments. (Pol) Syrowatka, T. (Zakład Toksykologii Sanitarnej, Państwowy Zakład Higieny, ul. Chocimska 24, 00-791 Warsaw, Poland); Tadeusiak, B.; Ladyga, M.; Jurek, A. *Roczn. Państw. Zakł. Hig.* 30(2): 179-184; 1979.

The effect of DDT (4,4'-Dichlorodiphenyltrichloroethane) on the mutagenic activity of 2-acetylaminofluorene (AAF) metabolites excreted in the urine was studied in Wistar rats. The mutagenic activity of the urine was determined with *Salmonella typhimurium* TA 1538 with or without incubation (60 min). In the acute experiment, the animals received single doses of DDT (100 mg/kg ip) and, 24 hr later, AAF (50 mg/kg ip). In the chronic experiment, the substances were administered in the food over 35 days; the doses were 50 mg/kg of food for DDT, and 300 mg/kg of food for AAF. In both experiments, urine of AAF-treated animals showed marked mutagenic activity. DDT caused a significant reduction in the urinary level of mutagenic metabolites in both the chronic and acute experiments. (17 refs)

- 79-4964 Mutagenic Activity of Propylene Oxide in Bacterial and Mammalian Systems. (Eng) Bootman, J. (Genetic Toxicology Labs., Life Science Res., Stock, Essex, England); Lodge, D. C.; Whalley, H. E. *Mutat Res* 67(2): 101-112; 1979.

Propylene oxide (PO) was studied for its ability to induce gene mutations and primary DNA damage in bacteria and chromosomal damage in mammalian cells. The induction of base-substitution mutations was demonstrated in spot tests with *Salmonella typhimurium* and *Escherichia coli* strains at 700 µg/plate of PO; inclusion of a preparation of rat liver microsomes and cofactors (S9 mix) had no significant effect on this response. A linear dose-response relationship was recorded in plate tests with *S. typhimurium* strains TA100 and TA1535 over the range 100-750 µg/plate. When added to dividing human lymphocytes in cultures, PO caused dose-related chromosomal damage, detected at 1.85 and 9.25 µg/ml. PO administration of the compound oxide at 2 x 100, 2 x 250, or 2 x 500 mg/kg to male CD-1 mice produced no detectable increases in the incidence of micronucleated, polychromatic RBC in bone marrow. In a male mouse dominant lethal test, PO doses of 50 or 250 mg/kg/day for 14 days gave no evidence of a mutagenic action on sperm. Ip injections of PO at 2 x 300 mg/kg increased the numbers of micronucleated RBC in mice, but lower doses given by this route had no such effect. Possible reasons for the contrasting findings in vitro and in vivo are discussed. (22 refs)

- 79-4965 Inhibition of Mono-oxygenase Activities by 1,1,1-Trichloropropene 1,2-Oxide, an Inhibitor of Epoxide Hydrase, in Rat Liver Microsomes. (Eng) Shimada, T. (Osaka Prefectural Inst. Public Health, Nakamichi, Higashinari-ku, Osaka 537, Japan); Sato, R. *Biochem Pharmacol* 28(11): 1777-1781; 1979.

The addition of 1,1,1-trichloropropene 2,3-oxide (TCPO), an inhibitor of microsomal epoxide hydrase, to Sprague-Dawley rat liver microsomes caused a type I spectral

change, the magnitude of which was increased by pretreatment of the animals with phenobarbital (PB: 100 mg/kg ip), but not with 3-methylcholanthrene (25 mg/kg ip) and polychlorinated biphenyls (100 mg/kg ip). TCPO inhibited aminopyrine N-demethylation competitively and prevented covalent binding of 2,4,2',4'-tetrachlorobiphenyl to macromolecules catalyzed by liver microsomes, although it stimulated benzo(a)pyrene hydroxylation significantly. It is suggested that TCPO interacts with cytochrome P-450, especially a species of the cytochrome that is inducible by PB, and thus inhibits monooxygenase activities of liver microsomes. (32 refs)

- 79-4966 Induction of Cholera Toxin Receptors in Cultured Cells by Butyric Acid. (Eng) Fishman, P. H. (Developmental and Metabolic Neurology Branch, Natl. Inst. Neurological and Communicative Diseases, NIH, Bethesda, MD 20205); Atikkan, E. E. *J Biol Chem* 254(11): 4342-4344; 1979.

Exposure of HeLa cells to sodium butyrate caused an increase in cholera toxin receptors as measured by increased binding of ¹²⁵I-cholera toxin to the intact cells. The process was dependent on time and butyrate concentration; maximal increases (over 40-fold) were observed at 48 hr and 5 mM sodium butyrate. Other short chain fatty acids were less effective in elevating cholera toxin receptors in the order: butyrate > pentanoate >> hexanoate > propionate. Acetate and isobutyrate had no effect. The increase in toxin receptors caused by butyrate was reversible and occurred in serum-free medium. The affinity of cholera toxin for control and butyrate-treated HeLa cells appeared to be similar. Butyrate also induced an elevation in cholera toxin receptors in rat C6 glial and Friend erythroleukemic cells but not in a butyrate-resistant HeLa mutant. The increase observed in Friend cells paralleled the increase in ganglioside GM1 (galactosylglucosylceramide), the reported cholera toxin receptor. Although no GM1 could be detected in untreated HeLa cells, small amounts were found in cells exposed to butyrate. (19 refs)

- 79-4967 In Vitro Transformation of Lung Cells of Young Hamsters by Chloro-2-butadiene. (Fre) Menezes, S. (Section de Biologie, Institut Curie, 26, rue d'Ulm, 75231 Paris Cedex 05, France); Papadopoulos, D.; Levy, S.; Markovits, P. *C R Acad Sci [D] (Paris)* 288(10): 923-926; 1979.

The carcinogenicity of 2-chlorobutadiene (CB, 1-500 µg/ml) was studied in vitro in normal hamster lung cell cultures. The carcinogenicity was determined from the take rate after intraocular transplantation of cells. While only 1 spontaneous tumor was found after the 33rd passage of untreated control cells, the take rates found after 5 and 13-14 passages of cells treated with 1 µg/ml concentration were

2/3 and 9/10, respectively. Further increase in the concentration did not increase the take rate. The tumors (fibrosarcomas, some of them showing signs of high malignancy) developed 17-62 days after grafting 10^3 - 10^5 cells. (5 refs)

79-4968 Reaction of Cyclohexane Oxides with Phosphodiester - Towards Understanding the Reaction of Benzo[a]pyrene Diol Epoxide with DNA. (Eng) Chan, T. H. (Dept. Chemistry, McGill Univ., Montreal, Quebec, Canada); DiRaddo, P. *Tetrahedron Lett* (22): 1947-1950; 1979.

The reaction of cyclohexene oxides (CO) with dialkyl and diaryl hydrogen phosphates (HP) was studied as a model for the reaction of benzo(a)pyrene (BP) diol epoxide with nucleic acids. CO reacted with a number of HP to give in good yield esters of *trans*-2'-hydroxycyclohexyl phosphate. CO also reacted with anilinium diphenyl phosphate in benzene to give an epoxide with a *trans*-opening. When phosphodiester were reacted with *cis*- and *trans*-cyclohexanol 2,3-oxide, the opening of the epoxides in all cases was a stereospecific *trans*-opening. The reaction was also regiospecific, with the phosphate attacking the 3' position. It is concluded that phosphodiester can be converted efficiently to phosphotriesters by CO and that the same conversion can be achieved with amine salts of the phosphates. Thus reaction of BP diol epoxide with nucleic acids is chemically feasible. Under acidic conditions, the presence of a neighboring hydroxy group appears to be sufficient to confer regiospecificity on the attack of the phosphate on the epoxide in an S(N)2 mechanism. (11 refs)

79-4969 Induction of Rat Liver Microsomal Enzymes by Cycloheximide. (Eng) Devasagayam, T. P. (Biology and Agriculture Div., Bhabha Atomic Res. Centre, Bombay 400 085, India); Pushpendran, C. K.; Eapen, J. *Biochem Pharmacol* 28(11): 1731-1734; 1979.

The effects of cycloheximide (2 mg/kg ip) on hepatic microsomal enzymes of female Wistar rats were studied. NADPH cytochrome c reductase of smooth microsomes and glucose-6-phosphatase of rough and smooth microsomes attained peak activities 2 hr after cycloheximide treatment. Cytochrome P-450 and cytochrome b₅ levels in the rough microsomes were highest 6 hr postinjection. On the other hand, the compound reduced ATPase activity in the smooth microsomes. All the components studied, except NADPH cytochrome c reductase of the smooth microsomes, approached control values 24 hr after the treatment. The rough and smooth microsomes differed in their responses to cycloheximide. The ATPase activity of the smooth microsomes declined more than that of the rough microsomes, whereas the levels of the mixed-function oxidases were generally higher in the smooth

microsomes. In addition, the decline in NADP cytochrome c reductase activity of the smooth microsomes was followed by a second increase in enzyme activity, with the result that enzyme levels were twofold higher than normal at 24 hr. (33 refs)

79-4970 Oxidative Deamination of Cyclohexylamine and Its Homologs by Rabbit Liver Microsomes. (Eng) Kurebayashi, H. (Dept. Medical Chemistry, National Inst. Hygienic Sciences, Kamiyoga, Setagaya, Tokyo, Japan); Tanaka, A.; Yamaha, T. *Biochem Pharmacol* 28(11): 1719-1726; 1979.

Cyclohexylamine (CHA) and its homologs cyclopentylamine (CPA) and cycloheptylamine (CHPA), which formed type II spectral changes in hepatic microsomes, were deaminated to the corresponding ketones by rabbit liver microsomes in the presence of NADPH and molecular oxygen. The alicyclic ketones were then reduced to the alcohols, in which the av percentages in the deaminated products were approx 75% CHA, 3% CPA, and 14% CHPA. The apparent Km's for these amines were 5.0 mM for CHA, 4.2 mM for CPA and 2.1 mM for CHPA; Vmax's were 11.0 (CHA), 42.1 (CPA) and 16.4 (CHPA) nmoles/mg protein/30 min. The deamination of these alicyclic primary amines was dependent on both NADPH and oxygen, and it was inhibited by carbon monoxide, SKF 525A, metyrapone, potassium cyanide, and mercuric chloride. These experiments indicate that the deamination of the alicyclic primary amines is catalyzed by a microsomal cytochrome P-450-dependent monooxygenase system in the rabbit liver. Cyclohexanone oxime and other oximes that were also identified in the incubation mixture may be intermediates of the microsomal deamination of alicyclic primary amines. (27 refs)

79-4971 Induction of Sister-chromatid Exchanges in Cultured Human Cells by an Organophosphorus Insecticide: Malathion. (Eng) Nicholas, A. H. (Center Human Genetics, Univ. Leuven, Minderbroedersstraat 12, B-3000 Leuven, Belgium); Vienne, M.; Van Den Berghe, H. *Mutat Res* 67(2): 167-172; 1979.

Because malathion is a widely used organophosphorous insecticide, the effects of nontoxic concentrations (2.5-40 µg/ml) on sister-chromatid exchange (SCE) frequencies were determined. Human fetal fibroblasts were exposed once or twice to malathion, with 20 hr between exposures. A single exposure to 40 µg/ml malathion resulted in a highly significant increase in the number of SCE's. After a double exposure, 20 µg/ml malathion induced an even greater increase in SCE frequencies. Comparison of these frequencies after single and double exposures indicated a cumulative effect; the number of SCE's at 5 µg/ml or

higher was significantly greater after the double exposure. An analysis of SCE's by chromosome group showed that exchanges were distributed approx according to chromosome length. (24 refs)

- 79-4972 Evaluation of Bravo, Phosdrin and Telvar as Possible Environmental Mutagens. (Eng) Kahlon, P. S. (Tennessee State Univ., Nashville, TN 37203); Banerjee, M. R. *Bull Environ Contam Toxicol* 22(3): 365-370; 1979.

The mutagenicities of three pesticides (Bravo, mevinphos, and monuron) for barley shoot tips (*Hordeum vulgare* cv. Trent) were studied. Bravo (250-1000 ppm) did not significantly increase chromosome aberrations, dicentric bridges, or multipolar anaphases and caused essentially no seedling injury as measured by growth. Mevinphos (250-1000 ppm) significantly increased chromosomal aberrations ($P < 0.01$), caused a high frequency of multipolar and polypoid anaphases, and caused 33%-40% seedling injury. It did not significantly increase dicentric bridges. Monuron (500-1000 ppm) significantly increased chromosome aberrations ($P < 0.01$), increased the frequency of dicentric bridges, and caused 17.2% (250 ppm) to 25.9% (500 ppm) seedling injury. (12 refs)

- 79-4973 Regenerative Proliferation of Mouse Epidermal Cells Following Application of a Skin Irritant (Cantharidin). Flow Microfluorometric DNA Measurements and [3 H]TdR Incorporation Studies of Isolated Basal Cells. (Eng) Clausen, O. P. (Inst. Forensic Medicine, Rikshospitalet, Oslo 1, Norway). *Cell Tissue Kinet* 12(2): 135-144; 1979.

Cantharidin (CTD), a strong skin irritant and a weak skin carcinogen, was applied in benzene soln to the backs of hairless mice (hr/hr Oslo strain). Single cell suspensions of epidermal basal cells were obtained and flow microfluorometric measurements of cellular DNA content were made. Smears were taken for autoradiography studies, and the [3 H]thymidine labeling index (LI) and mean grain count (MGC) were assessed up to 3 days after CTD application. Three successive peaks of cells with S-phase DNA content accompanied by three LI peaks were observed. The first two peaks were followed by peaks of cells in the G_2 phase, indicating that after the acute cell injury caused by CTD the cells traversed the cell cycle in partial synchrony through two subsequent cell cycles, each of 10-12 hr duration. During this phase of rapid proliferation, the LI reached the proportion of cells in the S-phase, contrary to what is observed in untreated mouse epidermis, where the labeled cells contribute to about half the proportion of cells with S-phase DNA content. The first two peaks of cells in the S phase and the LI coincided with an increased MGC, whereas the third peak was accompanied by a

MGC significantly below control values. This indicates that the latter peak is due to a longer DNA synthesis time rather than to a partially synchronized and increased cell proliferation. The duration of the G_1 , S, and G_2 phases seems to be reduced initially in rapidly proliferating epidermis. (32 refs)

- 79-4974 Redox Potential-dependent Nitrite Metabolism by *Salmonella typhimurium*. (Eng) Page, G. V. (Dept. Food Science, Cook College, Rutgers, The State Univ., New Brunswick, NJ 08903); Solberg, M. *Appl Environ Microbiol* 37(6): 1152-1156; 1979.

Studies demonstrating that *Salmonella typhimurium* is capable of metabolizing sodium nitrite are presented. Metabolism may take place by means of a nitrite-reducing enzyme function which is redox controlled. (24 refs)

- 79-4975 Sodium Nitrite and Sorbic Acid Effects on *Clostridium botulinum* Spore Germination and Total Microbial Growth in Chicken Frankfurter Emulsions During Temperature Abuse. (Eng) Sofos, J. N. (Dept. Food Science and Nutrition, Univ. Minnesota, St. Paul, MN 55108); Busta, F. F.; Allen, C. E. *Appl Environ Microbiol* 37(6): 1103-1109; 1979.

Clostridium botulinum spore germination occurred within 3 days following inoculation in both control and nitrite-treated mechanically deboned chicken meat frankfurter-type emulsions. Sorbic acid alone or in combination with nitrite significantly inhibited spore germination. A much longer incubation period was necessary for toxin formation in nitrite-sorbic acid combination treatments as compared with controls or nitrite and sorbic acid used individually. Total growth was unaffected by nitrite, whereas sorbic acid appeared to depress it. (24 refs)

- 79-4976 Subchronic Inhalation Toxicity of Nitromethane and 2-Nitropropane. (Eng) Lewis, T. R. (Natl. Inst. Occupational Safety and Health, Cincinnati, OH 45226); Ulrich, C. E.; Busey, W. M. *J Environ Pathol Toxicol* 2(5, Special): 233-249; 1979.

The subchronic inhalation toxicity of Nitromethane (NM) and 2-nitropropane (2-NP), two widely used industrial chemicals, was determined in order to recommend acceptable exposure levels in the workplace. Fifty male rats and 15 male rabbits were exposed to 98 or 745 ppm of NM or to 27 or 207 ppm of 2-NP 7 hr/day, 5 days/wk, for periods up to 24 wk. Fifty rats and 15 rabbits were exposed to filtered air for similar lengths of time, and they served as controls. Ten rats and five rabbits from each exposure and control

group were sacrificed at various times ranging from 2 days to 6 mo postexposure. Effects relatable to exposure to NM were a decreased body wt gain in rats following 8 wk of exposure to 745 ppm and a thyroid effect evidenced by an increased thyroid wt and decreased serum thyroxin levels. The latter was most notable in rabbits. Liver wts were significantly elevated in rats exposed to 207 ppm of 2-NP for 1, 3, and 6 mo. No exposure-related gross or microscopic alterations were seen in any of the tissues examined for rats and rabbits exposed to 98 or 745 ppm of NM and 27 ppm of 2-NP or in tissues of rabbits exposed to 207 ppm of 2-NP. Multiple hepatocellular carcinomas and numerous neoplastic nodules were seen in all 10 rats killed following 6 mo of exposure to 207 ppm of 2-NP, indicating that 2-NP is a potent carcinogen in the rat. (7 refs)

79-4977 Oral Chenodeoxycholic Acid Therapy and Colorectal Carcinoma: An Experimental Study. (Ger) Sauer, H. D. (Abteilung für Allgemeinchirurgie, Chirurgische Universitätsklinik, Martinstr. 52, D-2000 Hamburg 20, W. Germany); de Heer, K.; Mitschke, H. *Z Gastroenterol* 17(4): 236-243; 1979.

The effect of treatment with chenodeoxycholic acid (CDCA) on the carcinogenic activity of 1,2-dimethylhydrazine (DMH) was studied in young male Wistar rats. Twenty rats (Group 1) were treated with DMH (20 mg/kg/wk sc for 8 wk). Twenty other rats (Group 2) were treated with DMH in the same manner and also with CDCA (330 mg/100 g of diet, corresponding to 75 ± 25 mg po) during the same time. Twenty other animals (Group 3) were treated with CDCA only. All animals were sacrificed and examined 10 wk after the last DMH injection. The tumor frequency was 1/20 in Group 1 (adenoma), 3/20 (all carcinomas) in Group 2, and 0/20 in Group 3. All tumors were located in the descending colon. The findings indicate that the incidence of DMH-induced tumors following the simultaneous administration of CDCA is significantly increased and that patients treated with CDCA for radiolucent gallstones should be registered and followed up in order to gain definite information on its possible role as tumor promoter. (45 refs)

79-4978 Histopathological Studies on Experimentally Induced Pulmonary, Pleural and Peritoneal Neoplasms in Mice by Intraperitoneal Injection of Chrysotile Asbestos and N-Methyl-N-nitrosourea. (Eng) Kawai, T. (Dept. Pathology, Keio Univ. Sch. Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan). *Acta Pathol Jpn* 29(3): 421-433; 1979.

The cocarcinogenic effects of asbestos were studied following the administration of chrysotile asbestos (2.7 mg ip every 2 wk) and/or N-methyl-N-nitrosourea (MNU, 0.2 mg ip once weekly) for 22 wk to female dd mice. Multiple pulmonary adenomas (PA's) developed in 16/20 mice

given MNU alone, and 1 mouse developed a gastric leiomyosarcoma, 1 developed an intestinal fibrosarcoma, and 2 developed uterine carcinomas. In mice given chrysotile alone, cellular nodules developed on the serosa. A pleural tumor developed in one mouse and peritoneal tumors developed in two; neither asbestos fibers nor bodies were present in the pleural tumor. In mice given MNU plus chrysotile, 6/20 developed pulmonary carcinomas and 4/20 developed peritoneal tumors. The number of carcinomas/animal was greater and the latency time to tumor induction was smaller in this group than in the other two. This suggests that the chrysotile had a promoting or cocarcinogenic effect. A peritoneal tumor from the MNU plus chrysotile group was serially transplanted through nine passages in athymic nude mice. The original tumor and the transplanted tumors were all sarcomas of possible myogenic origin. (32 refs)

79-4979 Survival of Cells Implanted in the Embryonic Chick Limb Bud: A Difference Between Normal and Malignant Rat Brain Cells. (Eng) Tickle, C. (Dept. Biology as Applied to Medicine, Middlesex Hosp. Medical Sch., Cleveland St., London W1P 6DB, England); Crawley, A.; Roscoe, J. P. *J Cell Sci* 37: 143-156; 1979.

The fate of normal and malignant rat brain cells implanted in the embryonic chick limb bud was followed. Cells from normal rat brain tissue did not survive, and few cells could be found 1 day after grafting. In contrast, cells from a glioma and cells from a rat brain cultured 112 days after transplacental exposure to ethylnitrosourea survived well, and many mitoses were observed. These malignant cells also invaded the limb. The behavior of normal and malignant cells was followed at shorter times after grafting, and some invasion by the normal cells was detected. The first signs of normal cell degeneration were apparent around 7 hr after grafting, and after this the grafts progressively deteriorated. These results support the idea that the ability of cells to survive and grow in embryonic tissues is a characteristic of malignant cells. (32 refs)

79-4980 The Fine Structure of Stratified Ependyma in the Ventricular Wall of N-Ethyl-N-nitrosourea-treated Rats. (Eng) Pilkington, G. J. (Dept. Neurological Studies, Middlesex Hosp. Medical Sch., London W1P 8AA, England); Lantos, P. L. *Acta Neuropathol (Berl)* 46(3): 173-176; 1979.

Abnormal features in the ependymal lining of BD-IX rats treated transplacentally with N-ethyl-N-nitrosourea (ENU: 30 mg/kg, ip, on gestation day 15) were studied. Abnormal cell clusters and microtumors were found in and around the subependymal plate region from 8 wk of age onward. In one case, a tumor showing predominantly ependymal differentiation was observed. The ependymal cells at the inferior aspect of the lateral ventricles of 3/40 ENU-treated

rats formed a stratified lining composed of layers of well-differentiated ependymal cells up to 15 cells thick. In addition, there were ectopic ependymal cells dispersed haphazardly in the underlying neuropile. Occasionally, ectopic ependymal cells formed channels or cavities into which cilia and microvilluslike processes projected from the constituent cells. The cells showed no morphological signs of neoplastic transformation. None of the observed abnormalities were observed in untreated control rats. (10 refs)

- 79-4981 Prenatal Induction of Hepatocellular Glycogen Storage Areas and Tumors in Mice by Ethylnitrosourea. (Ger) Bannasch, P. (Abteilung für Cytopathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Mayer, D.; Venske, G. *Virchows Arch [Cell Pathol]* 30(2): 143-160; 1979.

Thirty-five C57/Bl₆ mice received a single dose of ethylnitrosourea (60 mg/kg ip) on day 16 of pregnancy. The livers of 65 male and 69 female offspring of the treated animals and of 63 male and 68 female offspring of untreated control mice were investigated for glycogen storage and neoplastic changes at different ages from 5 to 78 wk. In the experimental animals glycogen storage areas were found in 1/13 males and 0/13 females sacrificed at the age of 5 wk; in 0/4 males and 0/6 females at the age of 10 wk, in 3/13 males and 5/16 females at the age of 15-20 wk, in 9/9 males and 4/6 females at the age of 26 wk, in 5/22 males and 5/17 females at the age of 52 wk, and in 0/4 males and 0/11 females at the age of 78 wk. Glycogen-rich neoplastic nodules were found in experimental animals in 0/13 males and females each at the age of 5 wk, in 0/4 males and 0/6 females at the age of 10 wk, in 1/13 males and 0/16 females at the age of 15-20 wk, in 3/9 males and 0/6 females at the age of 26 wk, in 14/22 males and 7/17 females at the age of 52 wk, and in 2/4 males and 3/11 females at the age of 78 wk. Otherwise, no significant differences were found in the hepatic glycogen content between the experimental and control animals in the age bracket 15-20 wk. The first hepatocellular carcinomas were found at the age of 52 wk in both experimental males (15/22) and females (2/17). At the age of 78 wk, carcinomas were found in 4/4 males and 5/11 females. At the age of 26 wk, the hepatic glycogen content was significantly higher in the male experimental animals than in the male controls. The accumulated glycogen was found predominantly in the cytoplasmic matrix, sometimes in close contact with membranes of the agranular endoplasmic reticulum. Many cells of the neoplastic nodules contained liposomes and large spongy bodies in the dilated cisternae of the granular endoplasmic reticulum. Only 1 neoplastic nodule was seen in the controls. The findings indicate a close relationship between the development of prenatally induced hepatocellular tumors and focal hepatic glycogenosis in mice. (43 refs)

- 79-4982 Tumor Development in Lung of ddY Mice Following Transplacental Exposure to 1-Ethyl-1-nitrosourea. (Eng) Umezawa, I. (Kitasato Inst., Shirokane 5-9-1, Minato-ku, Tokyo 108, Japan); Komiyama, K.; Kawakubo, Y.; Nishiyama, Y.; Hata, T. *Gann* 70(3): 379-382; 1979.

A method for inducing lung tumors with 1-ethyl-1-nitrosourea (ENU) in 100% of experimental animals at almost the same time and within a short period was developed. Pregnant ddY mice were given a single ip injection of 58.5 mg/kg ENU between gestation days 13 and 19. Within 4-6 wk after birth, pulmonary tumor nodules were found in all offspring exposed to ENU. Histologically, they were found to be adenomas. The number of tumor nodules could be counted under the stereomicroscope starting around day 40 after birth. The size of the tumors increased with time, but the number of tumor nodules did not increase markedly. Weekly injections of urethan (0.5 mg/g ip, 0-3 wk after birth) or ENU (0.05 mg/g iv, 3-6 wk after birth) into mice pretreated with ENU during the fetal stage enhanced the number of pulmonary adenomas. The only other tumors that developed were a few lymphomas. Tumor development in the lung by injection of ENU in ddY mice during gestation is reproducible, relatively simple, and rapid. This method may be useful for the screening of antitumor agents. (13 refs)

- 79-4983 Comparison of Response of Fischer-344 and Charles River Rats to 1.5% Nitrilotriacetic Acid and 2% Trisodium Nitrilotriacetate, Monohydrate. (Eng) Anderson, R. L. (Miami Valley Lab., Procter & Gamble Co., Cincinnati, OH 45247); Kanerva, R. L. *Food Cosmet Toxicol* 17(2): 137-140; 1979.

The response of Charles River and Fischer-344 rats to dietary 1.5% nitrilotriacetic acid (NTA) and 2% trisodium nitrilotriacetate, monohydrate ($\text{Na}_3\text{NTA}\cdot\text{H}_2\text{O}$) were compared in a 4-wk feeding study. The Charles River rats consumed more NTA ($\mu\text{mol/kg}$ body wt/day) than the Fischer-344 rats. In spite of the different ingestion rates, the two strains gave similar qualitative responses to NTA. The ingestion of NTA was associated with reduced growth, increased kidney/body wt ratio, increased urinary Ca, hematuria, and the presence of crystalline CaNaNTA in the urine. These findings also applied to $\text{Na}_3\text{NTA}\cdot\text{H}_2\text{O}$; however, the incidence of hydronephrosis induced by this compound was greater in Charles River rats than in Fischer rats. (7 refs)

- 79-4984 1-Naphthylthiourea: A Mutagenic Rodenticide That Transforms Hamster Embryo Cells. (Eng) Kawalek, J. C. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Andrews, A. W.; Pienta, R. J. *Mol Pharmacol* 15(3): 678-684; 1979.

The mutagenicity of 1-naphthylthiourea (1-NTU) for *Salmonella typhimurium* strain TA 1538 and its ability to transform hamster embryo cells (HEC) were studied. 1-NTU was mutagenic when metabolized by liver microsomes from male Sprague-Dawley rats pretreated with Aroclor-1254 or phenobarbital. Two major fractions were separated by thin-layer chromatography (TLC): fraction A, which was not characterized, was only weakly mutagenic; and fraction B, which resembled 1-NTU, was as mutagenic without metabolic activation. At 1.0-25 $\mu\text{g}/\text{ml}$, 1-NTU also transformed HEC, but the individual TLC fractions transformed only at high concentrations. None of several other thiourea derivatives were mutagenic for *S. typhimurium* strains TA 1535 and TA 1538. Negative results were also obtained under conditions where a 1% level of contamination by 2-naphthylamine would have been detected. (23 refs)

79-4985 Interaction of Small Molecules with Phospholipid Bilayers. Binding to Egg Phosphatidylcholine of Some Uncharged Molecules (2-Acetylaminofluorene, 4-Dimethylaminoazobenzene, Estrone and Testosterone) That Bind to Ligandin and Aminoazo-Dye-binding Protein A. (Eng) Tipping, E. (Freshwater Biological Assoc., Ferry House, Ambleside, Cumbria LA22 0LP, England); Ketterer, B.; Christodoulides, L. *Biochem J* 180(2): 319-326; 1979.

The possible involvement of ligandin and aminoazo dye-binding protein A in intracellular transport was assessed by determining how their ligands, most of which are molecules with hydrophobic moieties, interact with cellular membranes. To obtain this information, the interactions of 2-acetylaminofluorene (AAF), 4-dimethylaminoazobenzene (DAB), estrone, and testosterone with aqueous dispersions of egg phosphatidylcholine and egg phosphatidylcholine/cholesterol (1:1 molar ratio) were examined by equilibrium dialysis and spectrophotometry. At 25 C and pH 7.4, the partition coefficients for binding to phosphatidylcholine [expressed as (mol of ligand bound/mol phosphatidylcholine)/unbound ligand concentration] were 5.0×10^3 , 2.1×10^4 , 3.1×10^3 , and 4.2×10^2 liters $\cdot\text{mol}^{-1}$ for AAF, DAB, estrone, and testosterone, respectively. In the ranges studied, these values were independent of concentration. The introduction of cholesterol into the lipid bilayers caused large decreases in the partition coefficients of estrone and testosterone, but had relatively little effect on the binding of AAF and DAB. By assuming that the interactions with egg phosphatidylcholine bilayers resemble those with the phospholipid components of mammalian intracellular membranes, the phosphatidylcholine partition coefficients, together with data for binding to the intracellular proteins ligandin and aminoazo dye-binding protein A, enable the subcellular distributions of the four components to be estimated. For the rat hepatocyte, up to 98%, 99%, 89%, and 58% of the total AAF, DAB, estrone and testosterone may be membrane-bound, respectively. (34 refs)

79-4986 Inhibition of RNA Synthesis by Derivatives of the Carcinogen 2-Acetylaminofluorene. (Eng) Austin, G. E. (Dept. Pathology, UCLA Sch. Medicine, Los Angeles, CA 90024); Moyer, G. H. *Proc Soc Exp Biol Med* 161(2): 220-224; 1979.

The mechanism by which N-hydroxy-N-2-acetylaminofluorene inhibits rat hepatic RNA synthesis was studied using the reactive ester N-acetoxy-N-2-acetylaminofluorene (N-acetoxy-AAF). Preincubation of isolated Sprague-Dawley rat nuclei with N-acetoxy-AAF (10^{-4} - 10^{-3} M) inhibited the ability of the nuclei to carry out RNA synthesis using an endogenous template or the exogenous template poly d(AT). Likewise, the template ability of DNA for RNA synthesis and the transcriptional capacity of RNA polymerases I and II were inhibited by preincubation of these macromolecules in vitro with N-acetoxy-AAF. Inactivation of enzyme or template by N-acetoxy-AAF was associated with and presumably caused by binding of AAF derivatives to these macromolecules. AAF binding required to inactivate polymerase or DNA in vitro was greater than that observed in vivo under conditions in which RNA synthesis was inhibited to a comparable extent, suggesting that additional mechanisms may operate in vivo to sensitize enzyme and template to inactivation by AAF binding. (18 refs)

79-4987 Application of ^{13}C and ^{15}N Spectroscopy to the Study of Electronic Delocalization in N-N Bonds: Nitrosamines, Hydrazones, Triazines and Related Protonated Species. (Eng) Gouesnard, J. P. (Chimie Organique Physique, ERA 312 CNRS, 2, rue de la Houssiniere, 44072 Nantes, France); Martin, G. J. *Org Magn Reson* 12(5): 263-270; 1979.

^{13}C and ^{15}N spectroscopy was used to study nitrogen lone-pair delocalization in N-N containing compounds: nitrosamines, nitramines, hydrazines, hydrazones, and triazines. Structure-chemical shift correlations were derived for nitrosamines, and equations were computed that permit the prediction of the electronic delocalization, expressed in terms of free enthalpy of activation. ^{15}N spectroscopy was also used to study the protonated species of nitrosamines and acceptor-donor complexes of nitrosamines with Lewis acids. (42 refs)

79-4988 Evaluation of Three Metabolic Activation Systems by a Forward Mutation Assay in *Salmonella*. (Eng) Pueyo, C. (Catedra de Genetica, Escuela Tecnica Superior de Ingenieros Agronomos de Cordoba, Cordoba, Spain); Frezza, D.; Smith, B. *Mutat Res* 64(3): 183-194; 1979.

Three mutagenicity assays, the intrasanguineous host-mediated assay (1), the microsomal assay in vitro (2), and

the isolated organ-mediated assay (3), were evaluated with the use of *Salmonella typhimurium araD531* strain SV3 as the indicator microorganism and dimethylnitrosamine (DMN) as the test substance. Forward mutations to L-arabinose resistance were selected in all assays. When SV3 was injected iv into male CD₁ mice, it disappeared rapidly from the bloodstream and was recovered mainly from the liver and, in smaller quantities, from the lungs and kidneys. No bactericidal action was found for up to 240 min of incubation. In assay 2, mutation induction was measured in bacteria recovered from the liver, lungs, and kidneys of CD₁ mice and CD rats treated with DMN (50-58 mg/kg via a metal cannula into the stomach). The frequency of forward mutations increased dramatically in these tissues. Liver bacteria had the highest mutation frequencies in most cases. The response was highest in the organs of female mice, followed by those in male mice and male rats. In comparison, assay 2 was relatively inefficient. Positive effects were restricted to mouse liver or kidney and rat liver microsomal preparations, and they did not surpass in vivo values, even with a 65-fold higher DMN concentration. In assay 3, bacteria recovered from rat liver perfused with 50 mM DMN showed an increased frequency (per 10⁶ cells) of 3,121 mutants, vs a control value of 10.6 mutants. In contrast, bacteria from the liver perfusate showed a mutation frequency of only 43 mutants. Bacteria recovered from rat lungs perfused with DMN showed a slight increase in mutation frequency that was only slightly above the value for the lung perfusate (43 and 10, respectively). The high sensitivity of assay 1 makes it useful for screening environmental mutagens. (33 refs)

- 79-4989 The Effect of Ammonium Sulfate on the Metabolism of Dimethylnitrosamine and Other Xenobiotics by Rat Hepatic Microsomes. (Eng) Lake, B. G. (British Industrial Biological Res. Assoc., Woodmansterne Rd., Carshalton, Surrey, SM5 4DS, England); Phillips, J. C.; Harris, R. A.; Gangolli, S. D. *Drug Metab Dispos* 7(3): 181-187; 1979.

The addition of 125-1,000 mM (NH₄)₂SO₄ to rat hepatic washed microsomal preparations markedly stimulated the rate of in vitro metabolism of the hepatocarcinogen dimethylnitrosamine. Solute treatment also stimulated the activities of NADPH-cytochrome c reductase, NADPH oxidase, the N-oxidation of N,N-dimethylaniline, and the fluorescent interaction of 8-anilino-1-naphthalenesulfonic acid (ANS) with hepatic microsomes. (NH₄)₂SO₄ had a varied effect on the activities of a number of mixed-function oxidase (MFO) enzyme activities. Whereas the activities of aniline 4-hydroxylase and 4-nitrobenzoic acid nitroreductase were enhanced at all solute concentrations, several other MFO enzyme activities were either progressively inhibited or stimulated at low and inhibited at high (NH₄)₂SO₄ concentrations. Solute treatment had no effect on microsomal cytochrome P-450 content but inhibited the activities of glucose 6-phosphatase and uridine

diphosphate-glucuronyltransferase. All of the observed changes in enzyme activities and ANS-microsome fluorescence interaction were found to be reversible when the solute was removed by centrifugation. These findings suggest that (NH₄)₂SO₄ and certain other solutes can reversibly modify the conformation of microsomal membranes in such a manner as to affect microsomal enzyme activities. (52 refs)

- 79-4990 Influences of Inducers and Inhibitors of the Microsomal Monooxygenase System on the Alkylating Intensity of Dimethylnitrosamine in Mice. (Eng) Appel, K. E. (Abt. Molekulare Toxikologie, Institut für Biochemie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Schwarz, M.; Rickart, R.; Kunz, W. *J Cancer Res Clin Oncol* 94(1): 47-61; 1979.

The effects of inducers [phenobarbital (PB) and 3-methylcholanthrene (3-MC)] and inhibitors (SKF 525A and CFT 1201) of the microsomal monooxygenase system on the alkylating capacity of ¹⁴C-diethylnitrosamine (¹⁴C-DEN, 10 mg/kg, ip) were studied in male NMRI mice. ¹⁴C-labeling of RNA and DNA was increased in mice pretreated with SKF 525A or CFT 1201 and decreased in mice treated with PB or 3-MC. Labeling of proteins was increased after pretreatment with any of the agents. Enhancement or reduction of specific activity occurred in all macromolecules to approx the same extent; no preferential alkylation of a particular cellular compartment was detected. In addition, no evident differences in the specific activities of the nucleic acids representing different cell compartments were detected. At the max alkylation time (approx 5 hr after DMN administration), incorporation of label into adenine and guanine was found in ribosomal RNA but not DNA. 1-Methyladenine could not be detected in DNA. It appeared that the changes in ¹⁴C activity were due to alterations in alkylating intensity and not to incorporation of labeled C₁-fragments. (41 refs)

- 79-4991 Comparative Studies of Neoplastic Response to a Single Dose of Nitroso Compounds. 6. The Effect of Diethylnitrosamine in Syrian Golden Hamsters. (Eng) Ii, Y. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE 68105); Pour, P.; Althoff, J. *J Cancer Res Clin Oncol* 94(1): 1-5; 1979.

The relationship between the effect of a single sc injection of different DEN doses (1.25, 2.5, 5, or 10 mg/kg) was examined in adult Syrian hamsters observed for life. The minimal effective dose (threshold dose) for a neoplastic response, reflected by the induction of papillary polyps in the larynx and/or trachea, was 1.03 mg/kg. The first neoplasm occurred at 19 wk in the highest dose group. No

treatment-related tumors were found in other segments of the respiratory epithelium or in other tissues. (10 refs)

- 79-4992 Antigen Characteristics of Nitrosamine-induced Urinary Bladder Cancer in Rats. (Eng) Hashimoto, Y. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan); Kitagawa, H. S. *Gann* 70(3): 305-314; 1979.

Tumor-associated or tumor-specific antigens expressed on urinary bladder cancer cells of transplantation and tissue culture lines that originated from tumors induced by N-butyl-N-(4-hydroxybutyl) nitrosamine in ACI/N rats were studied. Tumor-specific transplantation antigen was determined by the transplantability of cancer cells into syngeneic rats that had been immunized with the respective cancer cells. Two of six bladder cancer lines showed high tumor-specific transplantation antigenicity (H-A); the antigenicities of the other four lines were low or undetectable. Cross-resistance to transplantation immunity was observed in the two H-A lines but not in the other lines. Cell-mediated cytotoxicity was assayed by the micro-test plate method. Lymphoid cells from ACI rats hyperimmunized with cancer cells of a H-A line showed marked cytotoxicity against cancer cells of the immunizing line but not to cells of the other bladder cancer lines, including another H-A line that induced cross-resistance to transplantation immunity. Tumor-associated cell-surface antigen was detected by a membrane immunofluorescence test with serum that was raised in an allogeneic Donryu rat by the H-A bladder cancer and absorbed with normal ACI rat tissues. The absorbed serum gave positive membrane fluorescence to cancer cells of the immunizing line and two other bladder cancer lines but not to cells of the other four bladder lines and ACI tumors other than bladder cancer. The common antigen detected by the serological method was not reflected either in the transplantation immunity or cell-mediated cytotoxicity of the immune lymphoid cells. (25 refs)

- 79-4993 Animal Model: Carcinoma of the Urinary Bladder, Induced in Fischer Rats by N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide. (Eng) Cohen, S. M. (Dept. Pathology, St. Vincent Hosp., Worcester, MA 01604); Friedell, G. H. *Am J Pathol* 95(3): 849-852; 1979.

The development of carcinoma of the urinary bladder in male inbred Fischer 344 rats given N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT, 0.2% in the diet starting from weaning) is described. The FANFT-induced tumors resemble human bladder carcinoma in several ways. Most of the lesions are of transitional cell type and papillary, although most advanced tumors are polypoid masses protruding into the lumen (a fairly uncommon form of human

bladder cancer). As with the human disease, the FANFT-induced lesions progress from epithelial hyperplasia to noninvasive carcinoma, invasion, and eventually distant metastases. Hematuria is a frequent early sign in both species. Pleomorphic microvilli represent a marker of irreversibility in the rat bladder epithelium proliferation in response to the carcinogen, and comparable changes are seen in human tumors. Pleomorphic microvilli are also seen on exfoliated bladder epithelial cells from human and animal subjects. The rat model may be useful for the investigation of possible promoting and initiating agents. (11 refs)

- 79-4994 Chromosome Mutations and Chromosome Stability in Children Treated with Different Regimens of Immunosuppressive Drugs. (Eng) Schuler, D. (Second Dept. Paediatrics, Semmelweis Univ. Medical Sch., Budapest, Hungary); Dobos, M.; Fekete, G.; Miltenyi, M.; Kalmar, L. *Hum Hered* 29(2): 100-105; 1979.

The chromosome mutations and the number of sister-chromatid exchanges (SCEs) induced by different kinds of immunosuppressive drugs were investigated based on data from 43 children and five adults with renal disease and 19 control children. The number of chromosome aberrations after any treatment was higher than the pretreatment frequency. High doses of cyclophosphamide (CPA) or a combination vinblastine-CPA, chlorambucil 6-mercaptopurine (6-MCP), and prednisolone gave the highest frequencies of aberrations. High and low doses of all drugs except 6-MCP gave different effects. Increased SCE frequencies were found after treatment with high doses of CPA or 6-MCP. (24 refs)

- 79-4995 Acute Nonlymphocytic Leukemia (Letter to Editor). (Eng) Reimer, R. R. (Cleveland Clinic Foundation, Cleveland, OH 44106); Groppe, C. W. *Ann Intern Med* 90(6): 989; 1979.

A 56-yr-old woman who had received preoperative pelvic radiation (5,000 rads) for adenosquamous carcinoma of the endometrium followed postsurgery by doxorubicin and cyclophosphamide (totals of 700 and 12,600 mg, respectively, over 8 mo) developed acute myelogenous leukemia approx 1 yr after the chemotherapy was stopped. The leukemogenic potential of such combined modality therapy remains to be quantitated. (4 refs)

- 79-4996 Metronidazole Exhibits No Cytogenetic Effect in the Micronucleus Test in Mice or on Human Lymphocytes in Vitro. (Eng) Hartley-Asp, B. (Res. Labs., AB Leo, S-251 00 Helsingborg, Sweden). *Mutat Res* 67(2): 193-196; 1979.

The cytogenetic activity of metronidazole (MN) on peripheral human lymphocytes (PHL) in vitro and on mouse polychromatic erythrocytes (PE) in vivo was studied. PHL were incubated for 72 hr in the presence of MN (500, 1,000, or 10,000 $\mu\text{g}/\text{ml}$) or medium alone. At each concentration, 1,000 cells were analyzed for mitotic frequency and 100 metaphase plates for chromosome breakage. There was no significant difference in the mitotic index or the number of chromosome breaks between control and treated cells. NMRI mice received a total of 100-3,000 mg/kg MN (2 po doses 24 hr apart) and cytogenetic damage was evaluated by the micronucleus test. MN did not produce a micronucleus frequency outside that of the control range (0.09%-0.32%). Methylmethane sulfonate (positive control) produced sharp increases in micronucleus frequency at doses ranging from 40 to 100 mg/kg (2 ip injections 24 hr apart). The micronucleus frequency in the PE of mice given MN (700-7,000 mg/kg) in 7 po doses 24 hr apart did not exceed that of controls. It is suggested that the absence of cytogenetic damage in vivo and in vitro in mammalian and human cells may be due to generally ample oxygenation of normal cells and, therefore, a lack of active metabolites. (17 refs)

- 79-4997 Synthesis of α -Acetoxy-N-nitroso-4-[^3H]-pyrrolidine. (Eng) Saavedra, J. E. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Program, Frederick, MD 21701); Hecker, L. I.; Farrelly, J. G. *J Labelled Compd Radiopharm* 16(3): 415-420; 1979.

During studies of the chemistry and mechanism of carcinogenesis of nitrosopyrrolidine, it was necessary to prepare tritium-labeled α -acetoxy-N-nitroso-4-[^3H]-pyrrolidine (III) as a precursor to 2-hydroxy-4-[^3H]-tetrahydrofuran. The two-step synthesis of III from commercially available l-proline-4-[^3H](I) is described. I was nitrosated in aqueous hydrochloric acid to N-nitroso-4-[^3H]-l-proline (II). Decarboxylation of II with lead tetraacetate in methylene chloride at 45 C for 10 hr in 1.2 equivalents of pyridine gave III in an overall yield of 23%. The product was purified by silica gel column chromatography and further purified before use in the metabolic studies by high-pressure liquid chromatography. (11 refs)

- 79-4998 Induction of Sister Chromatid Exchanges in the Central Mudminnow Following In Vivo Exposure to Mutagenic Agents. (Eng) Kligerman, A. D. (Dept. Pathology, Duke Univ. Medical Center, Box 3156, Durham, NC 27710). *Mutat Res* 64(3): 205-217; 1979.

The central mudminnow (*Umbra limi*) was used as a model in vivo system to study sister-chromatid exchange (SCE) induction after ip administration of a direct-acting mutagen and a promutagen. In addition, mudminnows were used to

investigate SCE induction caused by the addition of a mutagenic dye to their laboratory aquatic environment. Five days after the injection of 500 $\mu\text{g}/\text{g}$ 5-bromodeoxyuridine, SCE rates were low in the gills (2.0-3.3 SCE's/metaphase), kidneys (2.6-3.4), and intestines (3.7-4.5). However, after injection of 5-103 $\mu\text{g}/\text{g}$ methylmethanesulfonate (MMS) or 0.3-22 $\mu\text{g}/\text{g}$ cyclophosphamide (CP), large, linear, dose-dependent increases in SCE rates were observed in all tissues examined. CP induced two to four times more SCE's than MMS. When neutral red dye was added to the aquarium water (0.01-12.5 ppm), the mudminnow concentrated the dye in its gill and kidney tissues. The dye caused significant increases in SCE rates at levels of <0.1 ppm. However, the dye concentration in the tissues did not correlate with SCE rate. In fact, the kidneys, which had the highest dye concentrations, had the lowest SCE rates of the tissues examined. The results demonstrate that the mudminnow can be used as a sensitive indicator of substances that induce SCE (31 refs)

- 79-4999 DNA Damage and Repair Induced by Diazoacetyl Derivatives of Amino Acids with Different Mechanism of Cytotoxicity. Correlations with Mutagenicity and Carcinogenicity. (Eng) Brambilla, G. (Istituto di Farmacologia, Universita di Genova, Viale Benedetto XV, 2, I-16132 Genoa, Italy); Cavanna, M.; Carlo, P.; Finollo, R.; Sciaba, L.; Parodi, S.; Bolognesi, C. *J Cancer Res Clin Oncol* 94(1): 7-20; 1979.

Eight synthetic N-diazoacetyl amino acids, prepared by inserting a diazoacetyl group onto the α -nitrogen of a natural amino acid, and two natural diazoacetyl amino acids, azaserine (O-diazoacetyl-L-serine) and 6-diazo-5-oxo-L-norleucine (DON), were studied autoradiographically for their capacity to induce DNA repair synthesis in BALB/c mouse kidney cells cultivated in vitro. Dose-dependent unscheduled DNA synthesis occurred in cells treated with the eight N-diazoacetyl derivatives, but not in cells exposed to approx equitoxic concentrations of azaserine and DON. Azaserine and DON, unlike the N-diazoacetyl derivatives, did not alkylate γ -(4-nitrobenzyl)pyridine to an appreciable extent. When DNA damage (single-stranded breaks or weak points in alkali) was measured by the sensitive alkaline elution technique, N-diazoacetyl-glycine amide was found to be about four times as potent as azaserine and about 12 times as potent as DON on a molar basis, but it was about 800 and 17,000 times as potent as azaserine and DON, respectively, by extrapolating to equitoxic concentrations. Carcinogenicity and mutagenicity seem mainly to be associated with the capacity for inducing DNA damage. (49 refs)

- 79-5000 Action of Nitrofurans on *E. Coli* Mutation and Induction and Repair of Daughter-Strand Gaps in DNA. (Eng) Lu, C. (Dept. Biochemistry, McMaster Univ., Hamilton, Ontario, Canada); McCalla, D. R.; Bryant, D. W. *Mutat Res* 67(2): 133-144; 1979.

In the "treat and plate" tryptophan reversion assay, the antibacterial and mutagenic potency of nine nitrofurans in *Escherichia coli* varied over almost 5 orders of magnitude. The relative toxicities were as follows: N-(5-nitro-2-furyl)-thiazolyl)formamide (FANFT) > 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF2) > 2-amino-4-(5-nitro-2-furyl) thiazole > furazolidine > furagin >> nitrofurantoin > nitrofurazone >> methylnitrofuroate >> nitrofuroic acid. In general, mutagenic activity paralleled toxicity. At concentrations corresponding to their LD50's, the compounds induced mutations at frequencies that ranged from $2.5/10^6$ survivors for FANFT to $130/10^6$ survivors for furagin (NF416). The observed differences in antibacterial and mutagenic activity are apparently not due to lack of activation of the weaker agents, since the two most potent agents were reduced somewhat more slowly than many of the less active agents. The relative sensitivities of AF2 of strains WP2, WP2 *uvrA*, CM561 (*lexA*) and CM571 (*recA*) to the antibacterial effects of AF2 were 1, 1.6, 3, and 7. With nitrofurazone, the relative sensitivities were 1, 1, 25, and 50. The *uvrA* strain was six- to sevenfold more mutable with both these agents than was WP2. No increase over the spontaneous mutation frequency was observed when *recA* or *lexA* strains were exposed to AF2 or nitrofurazone in these experiments. When wild-type or *uvrA* bacteria containing nitrofurantoin-induced lesions replicated their DNA in drug-free medium in the presence of [³H]thymidine for 5 min, the label was found in low mol-wt DNA, indicating that daughter-strand gaps were formed. During subsequent incubation in nonradioactive medium, the mol wt of the DNA increased to the control value. A *recA* strain (which was very sensitive to the lethal effects of AF2 and nitrofurazone) lacked the ability to repair daughter-strand gaps caused by nitrofurantoin-induced lesions. (26 refs)

- 79-5001 Production of Proliferative Lesions in Gastric Mucosa of Albino Mice by Oral Administration of N-Methyl-N'-nitro-N-nitrosoguanidine. (Eng) Sigaran, M. F. (Dept. Pathology, Sch. Medicine, Univ. Costa Rica at Hospital Mexico, San Jose, Costa Rica); Con-Wong, R. *Gann* 70(3): 343-352; 1979.

Ten groups of four Swiss albino mice were administered N-methyl-N'-N-nitrosoguanidine (MNNG: 100 µg/ml) in their drinking water for varying periods of time up to 68 wk, to determine whether there is a relationship between the quantity of mutagen ingested and the presence of proliferative mucosal lesions in the stomach or other lesions in various parts of the body. Intramucosal carcinomas occurred in 2/4 mice given MNNG for 68 wk, 2/4 mice given MNNG for 65 wk, and in 1/4 mice given MNNG for 54 wk. In the remaining groups of mice, which received MNNG for shorter periods of time, lesions occurred in a total of nine animals. These included foci of typical and atypical hyperplasia, erosion of the mucosa, and, in one animal, an adenomatous polyp. The lesions in all 10 groups did not demonstrate the sequence described by others; ie,

regenerative glandular hyperplasia, adenomatous hyperplasia, and adenocarcinoma. Beneath the diverse neoplastic lesions there was a predominantly inflammatory mononuclear infiltration with just a few polymorphonuclear cells. This response was not due to a local irritation caused by MNNG, and it was not present during the first weeks of the experiment. The reaction may represent an immunological response of the host to the development of neoplasia. Contrary to findings in humans, intestinal metaplasia preceding or accompanying the neoplasia was an inconsistent and infrequent alteration. (32 refs)

- 79-5002 Promotion of Epithelial Keratinization by N-Methyl-N'-nitro-N-nitrosoguanidine in Rat Forestomach in Organ Culture. (Eng) Fukamachi, H. (Zoological Inst., Univ. Tokyo, Tokyo 113, Japan); Takayama, S. *Experientia* 35(5): 666-668; 1979.

The effect of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG; 1, 3, or 5 µg/ml for 1 hr) on the epithelial differentiation of the fetal (16.5 days) rat (inbred Fischer 344/DuCrj strain) forestomach in organ culture was studied. In explants treated with 5 µg/ml MNNG, keratinization was first noted on day 3, and all the epithelium was keratinized on day 5. In explants treated with 3 µg/ml MNNG, epithelial keratinization was first noted on day 4, and the process of keratinization was completed on day 6. Explants treated with 1 µg/ml MNNG showed a time-course of epithelial differentiation similar to that of untreated control tissue. The data indicate that MNNG promotes epithelial differentiation in the fetal rat forestomach in organ culture. (7 refs)

- 79-5003 A ¹³C NMR Investigation of Restricted Rotation and Dimerization in p-Substituted Nitrosobenzenes. (Eng) Cox, R. H. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Hamada, M. *Org Magn Reson* 12(5): 322-325; 1979.

The barrier to internal rotation in a series of p-substituted nitrosobenzenes was determined by variable temperature ¹³C nuclear magnetic resonance. Substituent effects on the barrier were similar to those observed for acetophenones and benzaldehydes, and dimerization of the nitrosobenzenes was observed at low temperature for substituents CH₃, Cl, and H. The barrier height is discussed in terms of contributions from resonance effects. (28 refs)

- 79-5004 Enhancement of Reductive Metabolism of p-Nitrobenzoate and Nitrazepam in Isolated Perfused Rat Liver by Ethanol. (Eng) Jonen, H. G. (Dept. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany). *Drug Metab Dispos* 7(3): 176-180; 1979.

The reductive metabolism of p-nitrobenzoate in the isolated perfused rat liver was enhanced fivefold in the presence of 38 mM ethanol. Ethanol failed to increase hepatic nitroreduction when alcohol dehydrogenase activity was inhibited by pyrazole. Ethanol also enhanced the formation of the 7-amino derivative from nitrazepam, whereas the formation of 7-acetylamino derivative remained unchanged. (52 refs)

79-5005 Chemicals Which Revert All Commonly Used *Salmonella Typhimurium* Tester Strains. (Eng) McKee, R. H. (Litron Labs., 1351 Mt. Hope Avenue, Rochester, NY 14620); Tometsko, J. G.; Tometsko, A. M. *Mutat Res* 67(2): 183-187; 1979.

4-Fluoro-3-nitrophenylazide (FNPA) and dinitrophenyl azide (DNPA) induced reversions in five tester strains (TA98, TA100, TA1535, TA1537, and TA1538) of *Salmonella typhimurium* commonly used in the Ames test. FNPA and DNPA reverted the five strains in the dark, without the incorporation of liver microsomes; mutagenic induction was linear with all strains at FNPA or DNPA concentrations ranging from 100 to 400 µg/plate. At lower mutagen levels FNPA yielded 0.5 revertant per nanomole with TA100, (nmol) and DNPA yielded 10 revertants/nmol with TA98 and 5 with TA100. The reversion of TA100 and TA1535 by both FNPA and DNPA indicates a base-pair substitution mutagenic activity. The reversion of both the TA98/TA1538 pair and the TA1537 strain indicated frameshift-inducing mutagenic activity. FNPA or DNPA did not significantly enhance the reversion of the WP2s mutant of *Escherichia coli* at drug concentrations ranging from 1 to 400 µg/plate; this suggests that the base-pair substitution activity is restricted to specific types or sites. No enhancement of WP2s reversion in the presence of 40 µg sodium azide/plate was observed. These results suggest that the base-pair substitution mutagenic activity of FNPA and DNPA involves sites affected by sodium azide, whereas the frameshift mutagenic activity may be a more general effect. To rule out the possibility that the mutagenicity of FNPA and DNPA could be due to contamination with sodium azide, FNPA was repeatedly dissolved in ether, passed through a wool column, and dried. The purified material was significantly mutagenic. Conversely, when an equal amount of sodium azide was treated in the same way, the product showed no mutagenicity. Thus, the base-pair mutagenic activity is associated with FNPA rather than with a contaminant. (14 refs)

79-5006 Analgesic-associated Urinary-Tract Tumors (Letter to Editor). (Eng) Burnett, K. R. (Veterans Admin. Medical Center, Long Beach, CA 90822); Miller, J. B.; Greenbaum, E. *Ann Intern Med* 90(6): 994; 1979.

A Grade V transitional cell carcinoma was diagnosed in a 65-yr-old man who presented with a long history of phenacetin abuse and difficulty in voiding. Microscopic hematuria and pyuria plus kidney changes consistent with interstitial nephropathy were found initially. Four months later, total gross hematuria and a filling defect in the left renal pelvis were discovered. The tumor, which had an unusually rapid growth rate, may be partially or wholly due to the carcinogenicity of phenacetin. (2 refs)

79-5007 The Distribution of Carcinogens, 4-Nitroquinoline-1-oxide and 4-Hydroxyaminoquinoline-1-oxide, in the Nervous System and Its Possible Neurotoxicological Significance. (Eng) Takasu, T. (Dept. Neurology, Inst. Brain Res., Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan). *Experientia* 35(5): 668-670; 1979.

The distribution of the carcinogens 4-nitroquinoline-1-oxide (4NQO) and 4-hydroxyaminoquinoline-1-oxide (4HAQO) in the nervous system of adult male ddY mice following iv administration was studied. After 5 hr, the uptake of 4NQO by the CNS gray matter exceeded that by any other parenchymal organ and was much higher than that by the blood. The uptake by the cerebellar cortex and white matter was relatively low and that by the spinal dorsal root ganglia was quite low compared with the central gray matter. The uptake of 4HAQO by the brain and spinal cord was relatively low and that by the spinal dorsal root ganglia was high. The level of uptake by the trigeminal ganglia was also high. The results suggest that a considerable part of the 4NQO entering the CNS tissue parenchyma was taken up by the neuronal cell bodies, axons, and/or dendrites of the central gray matter. The data also suggest that 4HAQO and its metabolites in the blood cannot easily pass into the CNS tissue parenchyma. (9 refs)

79-5008 Effect of Aluminum Chloride on Binding of 4-Hydroxyaminoquinoline 1-Oxide to Nucleotides. (Eng) Yamane, Y. (Faculty Pharmaceutical Sciences, Chiba Univ., 1-33, Yayoi-cho, Chiba 260, Japan); Ohtawa, M. *Gann* 70(3): 361-364; 1979.

The effect of aluminum chloride (AC) and various other metals on the binding of 4-hydroxyaminoquinoline 1-oxide (4-HAQO) to dd mouse lung DNA, RNA, and various homopolyribonucleotides was examined in vitro, in the presence of seryl-AMP. AC markedly inhibited the binding of 4-HAQO to DNA, RNA, polyadenylic acid, and polyguanylic acid, resulting in binding rates that were 46%, 56%, 53%, and 18% of that of controls, respectively. The binding of 4-HAQO to polycytidylic acid and polyuridylic acid was not inhibited. Thus, the effect of AC is assumed to be due to an inhibition of the binding of 4-HAQO to purine base(s), especially guanine. Compared with the

other metals tested, AC had the strongest inhibitory effect, with the effects of the others decreasing in the order $\text{Cu}^{2+} > \text{Zn}^{2+} > \text{Mn}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+} > \text{Mg}^{2+}$. Fe^{3+} showed hardly any inhibition. It is concluded that inhibition of the binding of 4-HAQO to guanine is one of the factors in the inhibition of 4-nitroquinoline 1-oxide-induced lung cancer development by AC. (15 refs)

- 79-5009 The Application of Mitotic Gene Conversion in *Saccharomyces cerevisiae* in a Pattern of Four Assays, In Vitro and In Vivo, for Mutagenicity Testing. (Eng) Siebert, D. (Forstbotanisches Institut, Universitat Freiburg, Freiburg, E. Germany); Bayer, U.; Marquardt, H. *Mutat Res* 67(2): 145-156; 1979.

The induction of mitotic gene conversion of the nitrofurantoin derivatives nitrofurantoin (N-(5-nitro-2-furfuryliden)-1-aminohydantoin), nifurprazinum (1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazyl)-ethylenhydrochloride) and FANFT (2-formylamino -4-(5-nitro-2-furyl) thiazole) was investigated in the D4-RDII strain of *Saccharomyces cerevisiae* (heteroallelic at the gene loci *ade* and *trp5*, respiration-deficient). A battery of tests was applied: direct action of the substances in yeasts, the liver microsome test in vitro, the host-mediated assay, and the urinary assay. From the various combinations of positive and negative results, additional pharmacokinetic conclusions were drawn. The three nitrofurantoin derivatives gave positive results by direct action and in the urine of BDII rats. The addition of liver microsomes of NMRI mice in the in vitro test reduced the number of induced mitotic gene conversions. In the first hour, much of the nitrofurantoin given po to rats was excreted in the urine, as shown by a high genetic activity. Nifurprazinum and FANFT were excreted to a lesser extent or more slowly. Addition of glucuronidase/arylsulfatase reduced the genetic activity of nitrofurantoin in the urine, increased the activity of nifurprazinum, and was without any effect in the case of FANFT. In the host-mediated assay, only nitrofurantoin gave positive results. These results seem to be a consequence of the different excretion patterns of the nitrofurantoin derivatives. (31 refs)

- 79-5010 N-Nitroso Compound Contaminants in Prescription and Nonprescription Drugs. (Eng) Krull, I. S. (New England Inst. Life Sciences, 125 Second Ave., Waltham, MA 02154); Goff, U.; Silvergleid, A.; Fine, D. H. *Arzneim Forsch* 29(6): 870-874; 1979.

Gas chromatography-thermal energy analysis and high-pressure liquid chromatography-thermal energy analysis

revealed that N-nitroso compounds were not present in most of 73 pharmaceutical products tested. However, the analysis suggested the possible presence of N-nitroso impurities in three prescription drugs--phenylzine sulfate, imipramine HCl, and nitrofurantoin-- at levels of 81, 68, and 40 ppb, respectively, and in two over-the-counter cold remedies at 126 and 406 ppb. (17 refs)

- 79-5011 Carcinogenic Effect of 3-(Dihydroxymethyl)amino-6-(5-nitro-2-furylethenyl)-1,2,4-triazine Present in Panfuran-S in Mice. (Ger) Konishi, Y. (Dept. Oncological Pathology, Medical Univ., 840 Shi-jochi, Nara 634, Japan); Aoki, Y.; Takahashi, S.; Inui, S.; Denda, A.; Takita, M. *Onkologie* 2(1): 41-42; 1979.

The carcinogenicity of 3-(dihydroxymethyl)amino-6-(5-nitro-2-furylethenyl)-1,2,4-triazine (DHNT), present in the antimicrobial agent Panfuran-S, was studied in dd mice. The animals received Panfuran-S in the diet: the DHNT dose was 0 ppm in Group 1 (controls), 175 ppm in Group 2, 350 ppm in Group 3, 700 ppm in Group 4, 1,750 ppm in Group 5, and 3,500 ppm in Group 6. The tumor incidence was determined among survivors at 35 wk. The tumor incidence was 0 in the control group. Esophageal papillomas were found in 2/28 Group 5 and 4/17 Group 6 mice. Esophageal carcinomas were found in 3/28 Group 5 mice. Forestomach papillomas were found in 5/20 Group 2, 15/29 Group 3, 13/26 Group 4, and 4/28 Group 5 mice. Forestomach carcinomas were found in 3/29 Group 3, 9/26 Group 4, 20/28 Group 5, and 17/17 Group 6 mice. Adenocarcinomas of the duodenum and jejunum were found in Group 5 (8/28) and Group 6 (10/17). Gallbladder carcinomas were found in 2/28 animals in Group 5 and 1/17 in Group 6. The keratinizing squamous epithelial carcinomas showed numerous mitoses, and they metastasized into the liver, lungs, and regional lymph nodes and infiltrated the tissues surrounding the stomach and pancreas. The findings suggest that the carcinogenic effect of Panfuran-S is due to DHNT. (7 refs)

- 79-5012 Evaluation of the Mutagenicity of Aminoglycoside Antibiotics in *Salmonella typhimurium* and *Saccharomyces cerevisiae*. (Eng) Koeda, T. (Central Res. Labs., Meiji Seika Kaisha, Ltd., Morooka, Yokohama, Japan); Hirano, F. *J Antibiot (Tokyo)* 32(6): 607-609; 1979.

The aminoglycoside antibiotics kanamycin, aminodeoxykanamycin, dibekacin, ribostamycin, amikacin, gentamicin, and tobramycin were not mutagenic when tested in the *Salmonella typhimurium* and *Saccharomyces cerevisiae* systems. (5 refs)

- 79-5013 Intranuclear Rodlets in Undifferentiated Carcinomas of Salivary Glands in Strain A Mice in a Study Involving a Tobacco Specific Nitrosamine, N-Nitrosornicotine. (Eng) Hirota, N. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595). *Cancer Lett* 6(6): 365-369; 1979.

Strain A/J female mice (6-8 wk old) were injected with the tobacco-specific nitrosamine N-nitrosornicotine (NNN; 1 mg ip 3x/wk for 22 injections), and observed for 30 wk after the last injection. Salivary gland tumors which occurred in 2/44 mice, were examined by electron microscopy. Both tumors were undifferentiated carcinomas consisting of spheroidal and fusiform spindle cells. Ultrastructurally, distinctive intranuclear rodlets (INR) were observed in 1/5-10 cells. There were two types of rodlets; one was composed of fibrillar filaments arranged in bundles and the other was much thicker, branching in form without arrangement in bundles and was closely associated with nuclear chromatin or nucleoli. No rodlet-like inclusions were detected in other salivary tissues from either the NNN-treated or untreated groups and no viral particles were observed. The presence of INR in non-neuronal neoplastic cells may indicate a pathological process similar to nuclear body formation as seen in a variety of tumor cell types. (14 refs)

- 79-5014 Mutagenic Activity of Marihuana Smoke Condensates. (Eng) Busch, F. W. (Sch. Public Health, Univ. California, Berkeley, CA 94720); Seid, D. A.; Wei, E. T. *Cancer Lett* 6(6): 319-324; 1979.

The mutagenic activity of marihuana smoke condensates was evaluated in the Ames bioassay and compared to that of tobacco smoke condensates. Acetone extracts of uncombusted marihuana leaves were not mutagenic when tested, with and without liver homogenates (S-9) from Aroclor 124-pretreated rats, in *Salmonella typhimurium* strain TA98 at doses up to 1 mg/plate. Marihuana smoke condensates were mutagenic in TA98 in the presence of S-9. No significant mutagenic activity was observed in TA98 in the absence of S-9 or in strains TA1535 and TA1537, with and without S-9. The strain specificity indicates that frameshift mutagens were the predominant species. For standardized tobacco samples, marihuana condensates were approx 60% as mutagenic as tobacco condensates.

For freshly prepared samples, both were about equally mutagenic. It is concluded that the mutagenic activity of marihuana smoke condensates is comparable and certainly not greater than that of tobacco condensates. (18 refs)

- 79-5015 The Effects of Experimental Exposure to Tobacco Smoke on the Oxidative Metabolism of Alveolar Macrophages. (Eng) Drath, D. B. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA); Karnovsky, M. L.; Huber, G. L. *J Reticuloendothel Soc* 25(6): 597-604; 1979.

The effects of tobacco smoke on the oxidative metabolism and related enzymes of alveolar macrophages (AM) were studied. When exposed for 30 days to tobacco smoke, CD rat AM showed a doubling of oxygen consumption (QO_2) and hydrogen peroxide H_2O_2 release during phagocytosis. In addition, NADP⁺-dependent glucose oxidation was depressed although superoxide (O_2^-) release was unaffected. The glutathione cycle, thought to link peroxide-generating reactions with hexose monophosphate shunt activity, was unaffected by tobacco smoke. Glutathione peroxidase was present to the extent of 27.2 units/mg protein and 24.3 units/mg in the AM of control and smoke-exposed rats, respectively. The corresponding levels for glutathione reductase were 1.8 units/mg protein and 1.5 units/mg. A peroxidase similar to the myeloperoxidase of neutrophils was not detectable in AM. Catalase activity, although not affected by tobacco smoke, was present to the extent of 3.0 units/mg protein and was found in both a cytoplasmic and granule-rich component, with the latter latent to the extent of an order of magnitude. Superoxide dismutase activity was decreased 35% by smoke exposure. (31 refs)

- 79-5016 Effect of Smoking on the Recurrence of Malignant Melanoma. (Eng) Shaw, H. M. (Melanoma Clinic, Sydney Hosp., Macquarie St., Sydney, New South Wales 2000, Australia); Milton, G. W.; McCarthy, W. H.; Farago, G. A.; Dilworth, P. *Med J Aust* 1(6): 208-209; 1979.

The influence of smoking on the recurrence of malignant melanoma (MM) was studied in 1,908 Australian MM patients. At the time of diagnosis, 45.3% of the men and 28.1% of the women patients were smokers. Sites of primary lesions were similar in smokers and nonsmokers, but significantly more smokers than nonsmokers were <50 yr of age ($p < 0.01$ for men; $p < 0.001$ for women). There was a nonsignificant tendency for more smokers than nonsmokers to have regional lymph node or distant metastases at first presentation. Among the men with Stage

I MM diagnosis, the proportion of patients who were disease-free 5 yr later was significantly lower ($p < 0.02$) among smokers than nonsmokers (55% of 315 vs 63.0% of 403). A similar effect was not observed in the women patients. (8 refs)

- 79-5017 Carcinoma of the Larynx in Hamsters Exposed to Cigarette Smoke. Animal Model: Susceptible Inbred Line of Syrian Hamsters (BIO 15.16). (Eng) Homburger, F. (Bio-Res. Inst., Cambridge, MA); Soto, H.; Althoff, J.; Dalquen, P.; Heitz, P. *Am J Pathol* 95(3): 845-848; 1979.

The production of carcinoma of the larynx in susceptible inbred Syrian hamsters exposed to cigarette smoke is described. These cancers were indistinguishable by light microscopy from cancers of the larynx in heavily smoking human subjects. The same precancerous stages could be discerned in the lesions from both species. It may be assumed that the etiology of the cancers is the same in both species and the hamster model could be used to study alcohol as a cocarcinogen for laryngeal cancer. (12 refs)

- 79-5018 Implantation of Cigarette Smoke Condensate in the Lungs of Syrian Golden Hamsters. (Eng) Ketkar, M. B. (Abteilung für experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany); Haas, H.; Althoff, J. *J Cancer Res Clin Oncol* 94(1): 111-114; 1979.

The carcinogenic effects of benzo(a)pyrene (BP, 0.05 or 0.1 mg), cigarette smoke condensate (CSC, 50 mg), and the latter's nitromethane fraction (NMF, 5, 15, or 25 mg) were studied following the implantation of the substances in wax pellets in the lungs of male Syrian golden hamsters. There were no significant differences in survival rate or body wt after the different treatments. Round black or yellow nodules were found on the lung surface at the implantation site. A granulomatous inflammatory response was also observed at the site of implantation. Bronchiogenic adenomas developed in 1/31 animals given CSC and 5/63 animals treated with 15 or 25 mg NMF. Pleomorphic sarcomas, which spread throughout the lung and into the opposite lung, developed in 6/64 animals treated with BP. Tumors occurring at other sites were unrelated to treatment. (6 refs)

- 79-5019 Carcinogenicity of a Composite Organic Extract of Urban Particulate Atmospheric Pollutants Following Subcutaneous Injection in Infant Mice. (Eng) Epstein, S. S. (Sch. Public Health, Univ. Illinois Medical Center, Chicago, IL); Fujii, K.; Asahina, S. *Environ Res* 19(1): 163-176; 1979.

Studies of the carcinogenicity of atmospheric pollutants in mice were extended by investigating the effects of dose and time of administration of the extracts during the first 2 wk of life. Sc injection of a suspension of a composite organic (benzene) extract of particulate atmospheric pollutants into perinatal Swiss albino mice, at total doses of 5-40 mg, produced carcinogenic effects that were dose-related and related to the age of the mice at the time of injection. Injection within 1-7 days after birth resulted in a dose-related increase in the total tumor incidence and in the incidence of solitary pulmonary adenomas in both sexes. Additionally, the pollutant extracts induced multiple pulmonary adenomas, pulmonary adenocarcinomas, and lymphomas in males and females and hepatocellular carcinomas in males. The experiments indicated that 1- and 7-day-old mice are generally more sensitive than 14-day-old mice to carcinogens in organic extracts of air pollutants. (10 refs)

- 79-5020 Gas-Liquid Chromatographic Determination of Aniline Derivatives in Water. (Rus) Kulikova, G. S. (Inst. Chemistry, Ural Res. Center, Sverdlovsk, USSR); Kirichenko, V. E.; Pashkevich, K. I. *Zh Anal Khim* 34(4): 790-793; 1979.

A gas-liquid chromatographic assay for determining trace amounts of aniline derivatives in water is described. The compounds are extracted from water with benzene, converted into trifluoromethoxytetrafluoropropionic acid anilides, and chromatographed using a constant recombination-rate detector. The detection limit is 2.3×10^{-3} mg/liter, and the relative standard deviation is 0.02-0.04. (5 refs)

- 79-5021 Glutathione Adducts of N-Methyl-4-aminoazobenzene Formed In Vivo and by Reaction of N-Benzoyloxy-N-Methyl-4-aminoazobenzene with Glutathione. (Eng) Ketterer, B. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London W1P 7PN, England); Kadlubar, F.; Flammang, T.; Carne, T.; Enderby, G. *Chem Biol Interact* 25(1): 7-21; 1979.

The formation of an N-methyl-4-aminoazobenzene-reduced glutathione adduct following the administration of N,N-dimethyl-4-aminoazobenzene (DAB, 50 mg, ip) to bile-duct cannulated Wistar rats was investigated. The reaction of N-benzoyloxy-N-methyl-4-aminoazobenzene with glutathione in vitro yielded one major and two minor aminoazo dye-glutathione adducts. The major adduct was 3-(glutathion-S-yl)-N-methyl-4-aminoazobenzene (3-GS-MAB) and one of the minor products was 2'-(glutathion-S-yl)-N-methyl-4-aminoazobenzene. The other minor adduct was tentatively identified as 4'-(glutathion-S-yl)-N-methyl-4-aminoazobenzene. Two aminoazo dye derivatives were isolated from DAB-treated rats: 3-GS-MAB, and a probable 4-aminoazobenzene-glutathione adduct. (34 refs)

79-5022 Mutagenicity and Irreversible Binding of the Hepatocarcinogen, 2,4-Diaminotoluene. (Eng) Aune, T. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); Nelson, S. D.; Dybing, E. *Chem Biol Interact* 25(1): 23-33; 1979.

Mutagenicity of 2,4-diaminotoluene (DAT) in the *Salmonella* mutagenicity assay was increased with liver fractions from phenobarbital (PB) or β -naphthoflavone (BNF) treated rats. Substitutions of the hydrogens in the methyl group of 2,4-DAT with deuterium resulted in a decrease in mutagenicity. Incubation of rat liver microsomes with tritiated 2,4-DAT in the presence of NADPH led to the formation of irreversibly bound products to microsomal protein. The rates of binding were not increased using microsomes from PB or BNF-treated rats and was not altered by deuterium substitution in the methyl group. Addition of superoxide dismutase, glutathione (GSH) or rat liver supernatant reduced 2,4-DAT irreversible binding, whereas 2,4-DAT mutagenicity was unaffected by superoxide dismutase addition. Injection of tritiated 2,4-DAT 100 mg/kg to rats leads to its irreversible binding to liver protein and ribosomal RNA and to kidney protein in vivo. Protein binding was not increased after prior treatment with PB or BNF. No irreversible interaction of tritiated 2,4-DAT with DNA either in vitro or in vivo could be demonstrated. (24 refs)

79-5023 Neoplasms of the Forestomach in Mice Ingesting Dihydrosafrole. (Eng) Reuber, M. D. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701). *Digestion* 19(1): 42-47; 1979.

The max tolerated doses of dihydrosafrole, safrole, and isosafrole were given by continuous po administration, starting at age 7 days, to male and female mice of two hybrid strains, (C57BL/6 x C3HAnf)_{F1} and (C57BL/6 x AKR)_{F1}. Hyperplasia and carcinomas of the forestomach were significantly increased in female mice of both strains and in male C57BL/6 x AKR)_{F1} mice given dihydrosafrole. By contrast, forestomach neoplasms were not increased in mice receiving safrole or isosafrole. Mice with stomach neoplasms generally did not have liver neoplasms. (15 refs)

79-5024 Determination of the Tumorigenic Potential of Methylene-bis-ortho-chloroaniline. (Eng) Kommineni, C. (Natl. Inst. Occupational Safety and Health, Robert A. Taft Labs., 4676 Columbia Parkway, Cincinnati, OH 45226); Groth, D. H.; Frock, I. J.; Voelker, R. W.; Stanovick, R. P. *J Environ Pathol Toxicol* 2(5, Special): 149-171; 1979.

The dose-response effect of methylene(bis)ortho-chloroaniline (MOCA), a widely used industrial chemical, in male

Sprague-Dawley rats ingesting semipurified protein-adequate (PA) and protein-deficient (PD) diets was determined, and the amount of urinary MOCA excreted at various dose levels was correlated with tumor induction. MOCA induced a wide spectrum of neoplasms in male rats fed either the PA (27% casein) or the PD (8% casein) diet. The concentrations of MOCA used were 125, 250, 500, and 1,000 ppm. Increasing doses of MOCA in either diet resulted in decreased survival times. MOCA induced pulmonary adenomas, adenocarcinomas, mammary gland adenocarcinomas, Zymbal gland carcinomas, hepatocellular carcinomas, and hemangiosarcomas. In both diet groups, the lungs were the most sensitive organs to the induction of neoplasms by MOCA. The incidence of primary pulmonary neoplasms in the lowest dose group was 6% ($p \leq 0.01$), but in the highest dose group it was 70% ($p \leq 0.01$). The hepatocellular carcinoma incidence in rats fed a PD diet + 500 ppm MOCA was 18%, whereas the incidence in rats fed a PA diet + 500 ppm MOCA was only 4%. The mean urinary concentration of MOCA in rats fed the lowest dose (125 ppm-PD) was 0.63 ppm, a concentration comparable to that measured in the urine of workers exposed to MOCA. (5 refs)

79-5025 Study of the Inducing Action of Benzo-5,6-flavone on Pulmonary Benzo(a)pyrene Monoxidase Activity. (Fre) Queval, P. (Laboratoire de Pathologie pleuropulmonaire, Hopital Laennec, 42 rue de Sevres, 75007 Paris, France); Beaumatin, J. *C R Acad Sci [D] (Paris)* 288(15): 1215-1217; 1979.

The induction of pulmonary benzo(a)pyrene monoxidase (BMO) activity by benzo-5,6-flavone (BF) as well as by other substances and ionizing radiation was studied in 6- to 12-mo-old Sprague-Dawley rats. Compared with untreated controls [0.63 unit (U)], induction of BMO was seen in rats treated with BF (3-50 mg/kg ip, or 100 mg/kg/day po for 6 days: 9.03-17.53 U), benzo(a)pyrene (BP: 12.5 mg/kg: 14.49 U), methylcholanthrene (2.5 mg/kg: 13.33 U), or radiation (6,000 Working-Level-Month: 14.5 U). (A WLM = 168 hr spent in an atmosphere containing ^{222}Rn and its daughters at a concentration of 1 WL/m³. A WL = an atmospheric concentration of 10^{-7} Ci/m³ ^{222}Rn in equilibrium with its daughters.) Although tobacco smoke and flavone (20 mg/kg) did not induce BMO, they enhanced the enzyme-inducing effect of BF and BP. The findings indicate that the noncarcinogen BF is an excellent inducer of BMO activity. (10 refs)

79-5026 Mutagenicity of Quercetin and Kaempferol on Cultured Mammalian Cells. (Eng) Maruta, A. (First Dept. Internal Medicine, 3-46 Urafune-cho, Minamiku, Yokohama 232, Japan); Enaka, K.; Umeda, M. *Gann* 70(3): 273-276; 1979.

The mutagenicity of quercetin (QC) and kaempferol (KF) was investigated in V79 Chinese hamster cells, with and without metabolic activation. Treatment of the cells for 2 days with 10, 20, or 50 $\mu\text{g/ml}$ QC in the absence of metabolic activation produced slight growth inhibition; treatment of the cells with 20 or 50 $\mu\text{g/ml}$ KF produced severe growth inhibition. The number of 8-azaguanine-resistant colonies increased significantly after the cells were exposed to 20 or 50 $\mu\text{g/ml}$ QC, and mutation frequencies increased in a dose-dependent manner. With KF, mutation frequencies increased only slightly at 20 or 50 $\mu\text{g/ml}$. Treatment of the cells with QC in the presence of a metabolic activation system decreased the number of survivors and slightly increased the number of 8-AZ-resistant cells. The mutation frequency increased with dose, and it was 12 higher than that of control cultures at 200 $\mu\text{g/ml}$ QC. With KF, calculated mutation frequencies also increased with dose because of the marked decrease of survivors, although there was no increase in the number of resistant cells. QC was several times more active than KF in the metabolic activation assay. The results suggest that QC must be metabolized for it to exert its mutagenic activity and that the V79 cells themselves have an enzymic activation system that metabolizes QC very slowly but cumulatively. (6 refs)

- 79-5027 Cytogenetic Hazards from Agricultural Chemicals. (Eng) Panda, B. B. (Cytogenetics Lab., Dept. Botany, Berhampur Univ., Berhampur 760007, India); Sahu, R. K.; Sharma, C. B. *Mutat Res* 67(2): 161-166; 1979.

The responses of several mitotic systems to the β -exotoxin and δ -endotoxin protein from *Bacillus thuringiensis* were assayed as a sequel to test results of the exotoxin in *Allium*. The protein subunit of the δ -endotoxin had no effect on the root meristematic cells of *A. cepa*, *A. sativum*, or *Vicia faba*, with the exception of a mild mitodepression. The β -exotoxin, on the other hand, was C-mitotic in all these systems, and it also caused centromeric extension and clastogenesis in *A. sativum*. (29 refs)

- 79-5028 Mutagenic Activity of *Fusarium moniliforme* Isolates in the *Salmonella typhimurium* Assay. (Eng) Bjeldanes, L. F. (Dept. Nutritional Sciences, Univ. California, Berkeley, CA 94720); Thomson, S. V. *Appl Environ Microbiol* 37(6): 1118-1121; 1979.

A total of 33 isolates of *Fusarium moniliforme* from several food or feed crops were grown on sterile cracked corn, and chloroform-isopropanol extracts were assayed for mutagenic activity in the *Salmonella typhimurium*-microsome system. Tester strains TA98 and TA100 were used. Extracts of 21 of the isolates assayed against TA100 were mutagenic. The activities of seven of these extracts increased markedly with the incorporation of the liver

homogenate (S-9) into the assay. Seven of the 22 isolates assayed against TA98 were weakly active, with the liver homogenate having little effect on reversion rates. Isolation and characterization studies of the active compounds are in progress. (18 refs)

- 79-5029 Antibacterial Activity, DNA-attacking Ability and Mutagenic Ability of the Mycotoxin Zearalenone. (Eng) Boutibonnes, P. (Laboratoire de Physiologie bacterienne II, UER de Sciences, Univ. Caen, 14032 Caen Cedex, France); Loquet, C. *IRCS Med Sci (Cancer)* 7(4): 204; 1979.

In *Bacillus thuringiensis*, zearalenone induced cellular alterations and inhibited enzyme synthesis, sporulation, and growth rate. The mycotoxin also was positive in the *rec* assay (DNA-attacking ability) using *Bacillus subtilis*, but it was not mutagenic in the histidine(+) reversion assay using *Salmonella typhimurium*. (7 refs)

- 79-5030 The 'Carry-Over' of Aflatoxin, Ochratoxin and Zearalenone from Naturally Contaminated Feed to Tissues, Urine and Milk of Dairy Cows. (Eng) Shreeve, B. J. (Central Veterinary Lab., Weybridge, Surrey KT15 3NB, England); Patterson, D. S.; Roberts, B. A. *Food Cosmet Toxicol* 17(2): 151-152; 1979.

Concentrated rations containing 385-1,925 μg zearalenone/kg or 317-1,125 μg ochratoxin A/kg were fed to two cows for 7 and 11 wk, respectively. Aflatoxin B₁ was fortuitously present in both rations at a concentration of 20 $\mu\text{g/kg}$. Residues of zearalenone, ochratoxin A, and aflatoxin B₁ were not detected in muscle, liver, kidney, serum, milk, or urine, but ochratoxin A (5 $\mu\text{g/kg}$) was detected in the kidneys of one cow, and aflatoxin M₁ (trace amounts to 0.6 $\mu\text{g/kg}$) was detected in the kidneys, milk, and urine of all animals. (8 refs)

- 79-5031 Ammoniation of Aflatoxin Contaminated Corn in Diets for Growing Rats (Meeting Abstract). (Eng) Southern, L. L. (North Carolina State Univ., Raleigh, NC 27650); Clawson, A. J. *J Nutr* 109(6): 28; 1979 (no refs)

- 79-5032 Aflatoxin Contamination in Grains and Grain Products During the Dry Season in Guatemala. (Eng) de Campos, M. (Div. Food Control and Analysis, Inst. Nutrition Central America and Panama, Guatemala City, Guatemala); Olszyna-Marzys, A. E. *Bull Environ Contam Toxicol* 22(3): 350-356; 1979.

The incidence of aflatoxin contamination in grains and grain products obtained during the dry season in Guatemala was studied. Of the 264 samples analyzed, 17% were contaminated with aflatoxins and 8% exceeded the 20 ppb level of contamination. A greater incidence of contamination would be expected from samples collected during the rainy season. Aflatoxin B1 was found in all positive samples, aflatoxin G1 was found in corn, peanuts, rice, beans, and meat meal, and aflatoxin G2 was found only in rice and beans. The highest incidence of contamination (26%) was found in samples from the hot and humid region of the country compared with 7% contamination in samples from the hot and dry region and 2% contamination in samples from the cold or temperate and humid regions ($p < 0.05$). Moisture content of the samples was not correlated with aflatoxin contamination. The most important staple food, corn, showed 12% contamination; and rice, another staple, was also heavily contaminated. Only 1/26 samples of the second most important staple food, black beans, was contaminated. (17 refs)

79-5033 Impaired Phagocytosis by Heterophils from Chickens During Aflatoxicosis. (Eng) Chang, C. F. (Dept. Poultry Science, North Carolina State Univ., Raleigh, NC 27650); Hamilton, P. B. *Toxicol Appl Pharmacol* 48(3): 459-466; 1979.

The effects of graded concentrations of dietary aflatoxin (AF: 0, 0.625, 1.25, 2.5, 5.0, and 10.0 ppm) on the in vitro phagocytic and bactericidal abilities of heterophils from chickens were investigated. The mean, percentage, and rate of phagocytosis were reduced. Several heterophil populations were identified; 10% were unable to phagocytize (0 ppm), 15% were very sensitive to AF (0.625 ppm), 30% were resistant to AF (5 and 10 ppm), and about 45% were of intermediate sensitivity (1.25 and 2.5 ppm). Crossover experiments demonstrated that the cellular and serum factors required for optimal phagocytosis were impaired during aflatoxicosis and that the serum factor had the heat sensitivity of complement. Both spontaneous and chemotactic locomotion by heterophils were impaired. The heterophils from birds with aflatoxicosis that phagocytized bacteria had a reduced ability to kill the bacteria. Thus, a representative of the circulating phagocytes responsible in part for nonspecific host resistance has impaired function during aflatoxicosis. (40 refs)

79-5034 Portal Diversion Enhances Hepatocarcinogenesis Induced by Aflatoxin B₁ in the Rat (Meeting Abstract). (Eng) Franco, D. (Groupe de Recherche de Chirurgie hépatique, INSERM U17, Villejuif, France); Morin, J.; Torras, P.; Szekely, A. M.; Bismuth, H. *Digestion* 18(5/6): 425; 1978 (no refs)

79-5035 Transplantable Ileal Adenocarcinomas of ACI Rats. (Eng) Mori, H. (Dept. Pathology, Gifu Univ. Sch. Medicine, 40 Tsukasa-machi, Gifu 500, Japan); Tanaka, T.; Ushimaru, Y.; Kato, K.; Kawai, T.; Takahashi, M.; Hirono, I. *Gann* 70(3): 371-378; 1979.

Nine types of bracken-induced ileal adenocarcinomas were transplanted sc in ACI rats, and two of these were successfully established as transplantable tumor strains (designated 73-357 and 77-238). Ascitic conversion was successful in strain 73-357 only. Histological and electron microscopic findings are presented for the two tumor strains, which are the first transplantable ileal tumors to be described. (17 refs)

79-5036 Irreversibility of Degraded Carrageenan-induced Colorectal Squamous Metaplasia in Rats. (Eng) Oohashi, Y. (First Dept. Pathology, Sch. Medicine, Juntendo Univ., Hongo 2-1-1, Bunkyo-ku, Tokyo 113, Japan); Kitamura, S.; Wakabayashi, K.; Kuwabara, N.; Fukuda, Y. *Gann* 70(3): 391-392; 1979.

Male Sprague-Dawley rats fed a diet containing 10% degraded carrageenan (CG) for 1 day to 12 wk developed superficial hemorrhagic erosions and epithelial degeneration at the anorectal junction within 24 hr and squamous metaplasia of the rectal mucosa within 2 wk. The extent of involvement increased with the duration of CG administration. Colorectal metaplasia induced by 4-12 wk of CG feeding was still present upon examination of the rats 27 wk after the initial feeding, suggesting that irreversible squamous metaplasia is a precursor of the squamous cell carcinoma seen in laboratory animals with prolonged feeding of degraded CG. (5 refs)

79-5037 A Molecular Orbital Study on the Chemical Reactivity and Biological Activity of Polycyclic Aromatic Hydrocarbon Diol-Epoxides in Connection with Bay Region Theory. (Eng) Imamura, A. (Dept. Chemistry, Shiga Univ. Medical Science, Setatsukinowacho, Otsu, Shiga-ken 520-21, Japan); Koda, M.; Kato, S. *Gann* 70(3): 291-296; 1979.

A molecular orbital method was applied to several polycyclic aromatic hydrocarbon diol-epoxides to study the role of the bay region in their biological activity and chemical reactivity. Electronic structures of naphthalene, anthracene, phenanthrene, and benzo(a)pyrene diol-epoxides were calculated by a combination of the CNDO/2 (complete neglect of differential overlap) and energy minimization methods. With these methods, the most stable molecular geometry was obtained automatically. By comparing the total energy of phenanthrene diol-epoxide with that of anthracene diol-epoxide, the role of the bay region was studied in connection with chemical reactivity. It was concluded that the bay region plays an important

role when the diol-epoxide reacts with a component of the biological system via an SN1 mechanism. Moreover, benzo(a)pyrene diol-epoxide was shown to be very reactive because it contained a bay region and because of its large size. When reaction proceeded via an SN2 mechanism, the bay region had little effect on the chemical reactivity of the molecules. (21 refs)

79-5038 Quantum Chemical Studies of the Metabolism of Polycyclic Aromatic Amines and the Stabilities and Electrophilicities of Their Arylnitrenium Ions in Relation to Their Mutagenic/Carcinogenic Potencies. (Eng) Loew, G. H. (Molecular Theory Lab., Dept. Genetics, Stanford Univ. Medical Center, Stanford, CA 94305); Phillips, J.; Pack, G. *Cancer Biochem Biophys* 3(3): 101-110; 1979.

Electronic parameters related to the cytochrome P450-catalyzed reactions of eight polycyclic aromatic amines were calculated using all valence electron semiempirical molecular orbital methods. Parameters were calculated related to the relative ease of metabolic transformation of each parent compound to hydroxylamines by cytochrome P-450 and to other competing metabolic products involving ring epoxidation and hydroxylations. The eight compounds studied were 2-amino naphthalene, 1-amino naphthalene, 2-amino fluorene, 4-amino fluorene, 2-amino anthracene, 1-amino anthracene, 1-amino pyrene, and 6-amino chrysene. The calculations indicated that as the size of the ring system increases, the aryl nitrenium ions become more stable relative to the N-hydroxylamines and their esters, with the possible exception of 1-N-hydroxynaphthylamine which is predicted to form a more stable nitrenium ion than the aminofluorenes. For the four pairs of compounds studied, the parent compound which was predicted to form more hydroxylamine is the more potent mutagen and carcinogen. Considering competing ring metabolite formation, the less potent isomer has the ring carbon which is most reactive to direct phenol formation. Thus, direct phenol formation appears to be an effective detoxification pathway. Ring epoxidation, however, appears to be more activating than detoxifying. The results verify that hydroxylamine formation and the electrophilicity of aryl nitrenium ions are important steps in determining relative mutagenic activity of polycyclic aromatic amines and lead to calculated parameters which can monitor these steps and predict relative activity. (44 refs)

79-5039 Cimetidine and Gastric Cancer (Letter to Editor). (Eng) Roe, F. J. (4 Kings Road, Wimbledon SW19 8QN, England). *Lancet* 1(8124): 1039; 1979.

A long-term study in rats showed no increased risk of gastric malignancy due to cimetidine (Tagamet), which was administered at doses >60 times those used clinically. Of

the three reported cases of gastric cancer in cimetidine users, the interval from first exposure to diagnosis ranged from 10 wk to 11 mo. Thus, a causative link is highly improbable. (4 refs)

79-5040 Gastric Cancer in Patients Who Have Taken Cimetidine (5 Letters to Editor). (Eng) Rudell, W. S. (Dept. Medicine, St. James's Hosp., Leeds LS9 7TF, England); Reed, P. I.; Cassell, P. G.; Walters, C. L.; Hill, M. J.; Taylor, T. V.; Lee, D.; Howatson, A. G.; Anderson, J.; MacLeod, I. B.; Rubin, P. *Lancet* 1(8128): 1234-1236; 1979.

Several letters were written in response to a recent article stating that there was an association between cimetidine therapy and gastric cancer in three patients. The occurrence of gastric cancer in three additional patients on long-term cimetidine therapy for duodenal and/or gastric ulcer is reported. It is suggested that cimetidine may both mask the symptoms of gastric cancer and contribute to its development. However, it is only one of many drugs and dietary factors that are potentially nitrosatable under gastric conditions, and there is no good reason for singling out cimetidine as a unique hazard. The fact that the latency period between onset of treatment and diagnosis of carcinoma in the three original patients was only 6-12 mo suggests that these cancers were not in fact due to cimetidine. Furthermore, it is not known whether these patients had neoplastic changes before cimetidine treatment. (11 refs)

79-5041 The Carcinogenic Effect of TPA (12-O-Tetradecanoylphorbol-13-Acetate) When Applied to the Skin of Hairless Mice. (Eng) Iversen, U. M. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway); Iversen, O. H. *Virchows Arch [Cell Pathol]* 30(1): 33-42; 1979.

The carcinogenic effect of topical 12-O-tetradecanoylphorbol-13-acetate (TPA) was studied in hairless mice given 1, 2, 5, or 50 applications of 20 nanomoles (nmoles) of TPA and observed for 83 wk. In mice receiving 20 nmoles of TPA, one squamous cell carcinoma and one angiosarcoma of the spleen were detected, both in females. In the group painted twice with TPA there were three skin tumors (2 females, 1 male), one sarcoma of the dermis (female), and one sc myxosarcoma (female). Four skin tumors appeared in males and one in a female of the group painted five times. Three male mice had sarcomas of the dermis, and in female mice there were two benign angiomas of the liver, two granulosa cell tumors, and one thecoma of the ovaries. In the group painted 50 times, there were four skin tumors in male mice and three in females. One male and three females developed squamous cell carcinomas. One male had a malignant hepatoma, one a myxosarcoma in the abdominal cavity, and one an angiosarcoma of the thyroid. Two females had angiosarcomas of the spleen and soft tissues and one an adenocarcinoma in the omentum.

Reticuloses, which are common in hairless mice, were seen in each treatment group. The yield of skin carcinomas (4/19) in the group given 50 applications was significantly greater than in mice given ≤ 5 applications. This increase in response with dose is evidence for the carcinogenic activity of TPA. The compound should be regarded as a complete carcinogen. (18 refs)

- 79-5042 Erythroleukemia in a Renal Transplant Recipient. (Eng) Ellerton, J. A. (Dept. Medical Oncology, New England Medical Center, 171 Harrison Ave., Boston, MA 02111); deVeber, G. A.; Baker, M. A. *Cancer* 43(5): 1924-1926; 1979.

A case of erythroleukemia (EL) in a renal transplant recipient receiving long-term azathioprine therapy is reported. A 53-yr-old man developed acute EL 3 yr after renal transplantation. He had received 3 yr of immunosuppressive therapy with azathioprine (3 mg/kg/day). A preleukemic phase associated with chromosome abnormalities (consistent deletion of B-5; deletion of E-17 or a D group chromosome) was recognized. Repeat cytogenetic studies 4 mo later revealed the same B group deletion plus a G group deletion and duplication of the short arm of E-17. Azathioprine has been associated with chromosome abnormalities. Chronic stimulation of an abnormal erythroid clone by the transplantation may have hastened the development of EL. (20 refs)

- 79-5043 Chloramphenicol and Chromosomal Morphology. (Eng) Goh, K. (Univ. Rochester and Monroe Community Hosp., Rochester, NY 14603). *J Med Clin Exp Theor* 10(3): 159-166; 1979.

The effect of chloramphenicol (CM) on the chromosomes of cultured peripheral blood lymphocytes from two normal donors was studied. Ten 10-ml cultures were made from each donor. A dose of 800 μ g CM was added to two phytohemagglutinin-stimulated WBC cultures from each donor at the various stages of the cell cycle. The cultures were terminated for chromosome analyses. More abnormalities were seen in the CM-treated cultures than in the control cultures (treated with solvent alone). The highest incidence was seen when CM was added at G₀, the lowest incidence when CM was added at G₂. These results correlate well with the percentage of protein synthesis and transport to the acidic residual chromosomal protein fraction previously determined in HeLa S-3 cells. It is concluded that CM is capable of inhibiting protein synthesis, which results in a chromosome protein deficiency. This deficiency produces a "weakness" in the chromosome backbone. (14 refs)

- 79-5044 Binding of Polycyclic Aromatic Hydrocarbons to DNA of Cells in Culture: A Rapid Method for Its Analysis Using Hydroxylapatite Column Chromatography. (Eng) Shoyab, M. (Meloy Labs., Inc., 6715 Electronic Drive, Springfield, VA 22151). *Chem Biol Interact* 25(1): 71-85; 1979.

A rapid procedure to study the interaction of carcinogens with DNA in cultured cells has been developed. The cells, which are labeled with 7,12-³H]dimethylbenz[a]anthracene (³H]DMBA), are lysed with 0.24 M phosphate buffer (pH 6.8), 1% sodium dodecyl sulfate (SDS), 8 M urea and 0.01 M ethylenediamine-tetraacetate (EDTA) and sonicated. The cell lysates are fractionated on columns of hydroxylapatite. Proteins and RNA are removed with 8 M urea in 0.24 M phosphate buffer (pH 6.8). DMBA-bound DNA is eluted with 0.4 M phosphate buffer (pH 6.8). DMBA-DNA isolated by this procedure is virtually free from proteins and RNA. Thermal stability, ultraviolet spectra and the density of DNA are not altered by DMBA binding. The uptake of DMBA by mouse epidermal cells is rapid, and the binding of DMBA to DNA is linear for the first 8 hr of exposure. DMBA binds to DNA in all phases of the cell cycle. However, the highest binding occurs immediately following maximum DNA synthesis. (26 refs)

- 79-5045 Non-immunological Regression of Dimethylbenz(a)anthracene-induced Experimental Keratoacanthomas in the Rabbit. (Eng) Ramselaar, C. G. (Dept. Dermatology, St. Antonius Hosp., Jan van Seorelstraat 2, Utrecht, Netherlands); van der Meer, J. B. *Dermatologica* 158(2): 142-151; 1979.

Immunofluorescence studies and skin tests with autologous tumor extracts were performed in New Zealand white rabbits to determine the possible immune-mediated factors involved in the spontaneous regression of keratoacanthomas induced by 7,12-dimethylbenz(a)anthracene (DMBA). These tumors grow rapidly, reaching max size in a few weeks, and they resolve spontaneously without treatment. Nine rabbits were shaved weekly and the shaved area was pencilled with a 1% soln of DMBA in lanolin with 3% soft paraffin. Pencilling was stopped when a rabbit showed the first tumor: after 10-15 wk, all nine experimental rabbits had tumors (total, 17). Nine rabbits served as controls. Immunofluorescence studies revealed that there were no specific staining patterns in any of the 17 keratoacanthomas. No tumor-specific antibodies were detected. There were no immediate or delayed cutaneous hypersensitivity reactions to injections of tumor extract and normal rabbit skin. The results of this study do not implicate the immune system in keratoacanthoma regression. (26 refs)

- 79-5046 Effects of LS 1727, a Nitrosocarbamate of 19-Nortestosterone, on Dimethylbenz(a)anthracene-induced Mammary Tumors in the Rat. (Eng) Bouveng, R. (Research Labs., AB Leo, S-251 00 Helsingborg, Sweden); Ellman, M.; Gunnarsson, P. O.; Jensen, G.; Liljekvist, J.; Muntzing, J. *Eur J Cancer* 15(4): 407-414; 1979.

The effect of LS 1727, a nitrosocarbamate of 19-nortestosterone, on mammary tumors induced by dimethylbenz(a)anthracene (DMBA) was studied in virgin female Sprague-Dawley rats. Fifty-day-old animals were given 20 mg DMBA po and 7 wk later were examined for tumors. Animals with 1-5 tumors, at least one of which was >10 mm diameter, were studied. The rats were injected with LS 1727 (0.31, 1.25, 10, 20, or 40 mg/kg ip 1x/day for 4 wk) and the tumors measured for 4 wk following the treatment period. LS 1727 caused a dose-dependent reduction in tumor growth. Even at the 0.31 mg/kg dose the effect was significant. Neither 19-nortestosterone nor 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea (CCNU), a compound with structural similarity to the alkylating moiety of LS 1727, had any significant effect on tumor growth. LS 1727 administration reduced the uptake of radioactivity in the tumors after injection of (³H) dihydrotestosterone but not after injection of (³H) estradiol-17 β or (³H) progesterone. There was no accumulation of radioactivity in the tumors after injection of (³H)-LS 1727. Thin layer chromatography revealed that LS 1727 is rapidly metabolized (<30 min) to 19-nortestosterone and polar metabolites. These results show that LS 1727 has a growth-inhibitory effect, probably exerted by both an alkylating and a hormonal action of the compound, on DMBA-induced mammary tumors. (23 refs)

- 79-5047 Prolactin Receptors in Primary Cultures of Carcinogen-induced Rat-Mammary Tumors. (Eng) Costlow, M. E. (Dept. Biochemistry, St. Jude Children's Res. Hosp., 332 N. Lauderdale, Memphis, TN 38101); Gallagher, P. E.; Koseki, Y. *Mol Cell Endocrinol* 14(1): 81-97; 1979.

Some of the conditions, including those for tumor cell dissociation, that influence the growth of mammary tumor cells and the concentration of prolactin (PRL) binding sites in vitro are presented. 7,12-Dimethylbenz(a)anthracene-induced Sprague-Dawley rat mammary tumors were dissociated with collagenase and hyaluronidase and placed into primary culture. In most cultures, specific binding of ¹²⁵I-labeled ovine PRL was (1) lower than that for the original tumors unless bovine PRL (1 μ g/ml) had been added to the dissociation medium and (2) varied with the type of growth medium used. The level of PRL binding in cultured cell homogenates was relatively constant for the first 7-10 days. PRL binding in cultured cell homogenates was max at pH 7.0, proportional to cell protein, specific for PRL, and reached a steady state by 12 hr at 22 C. The

half-max inhibition of ¹²⁵I-labeled PRL binding by unlabeled PRL was 100 nanograms(ng)/ml for cells grown in 5-1,000 ng PRL/ml. After PRL was removed from the growth medium, the level of available binding sites progressively increased, reached a max at 48 hr, and then declined. At 48 hr, the dissociation constant for PRL binding (Kd approx 1×10^{-10} M) was comparable to that in the tumors. In some cultured tumors, a 48-hr treatment with 0.5 or 1.0 ng PRL/ml increased the level of PRL binding. PRL increased DNA synthesis, and its removal reduced [³H] estradiol and [³H] R5020 binding to cultured cell cytosols. (32 refs)

- 79-5048 Studies on the Formation of Lipophilic Derivatives of the Chemical Carcinogen 7,12-Dimethylbenz(a)anthracene In Vivo. (Eng) Khanduja, K. L. (Dept. Biophysics, Postgraduate Inst. Med. Educ. Res., Chandigarh, India). *Bull Postgrad Inst Med Educ Res Chandigarh* 12(3): 144-149; 1978.

The composition and the amount of lipophilic derivatives of 7,12-dimethylbenz(a)anthracene (DMBA, 2 mg, iv) in various organs was studied using virgin female Wistar rats. In all organs except the mammary gland, radioactivity associated with ³H-DMBA was maximal at 5 min. DMBA continued to accumulate in the mammary gland for 1.5 hr. The concentrations decreased rapidly with time in the liver, kidney, spleen, and blood. Liver lipid elution profiles revealed the presence of two peaks. Similar peaks were observed with the splenic lipids. The concentration in kidney lipids was low and no significant concentration of slowly excreting derivatives in the mammary gland was observed. Further investigations are required in order to understand the role of these derivatives in DMBA-induced mammary gland carcinogenesis. (10 refs)

- 79-5049 The Effect of Hydroxylamine on the Morphology of the Rat Mammary Gland and on the Induction of Mammary Tumors by 7,12-Dimethylbenz(a)anthracene. (Eng) Poukka-Evarts, R. (Lab. Carcinogen Metabolism, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20205); Brown, C. A.; Atta, G. J. *Exp Mol Pathol* 30(3): 337-348; 1979.

The effect of hydroxylamine (HA) on the morphology of rat mammary gland and on the formation of mammary tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA) was studied in virgin female Sprague-Dawley rats. The rats were divided into five groups and were given HA sulfate in drinking water as a 10 mM soln, (Group 2), or 11 mg DMBA in corn oil po through a stomach tube, (Group 5). Groups 3 and 4 received a combination of HA and DMBA. Groups 1 (control) and 5 received tap water throughout the experiment. Tumors first appeared 18 days after DMBA administration among Group 3 rats who had received HA for 14 days prior to DMBA administration.

Among animals in Group 4, where HA administration was started 2 wk after DMBA administration the first palpable tumors appeared at the same time as among DMBA only treated animals (Group 5). The mean latency period, 102.4 days, for Group 4, which was given HA after DMBA, was significantly greater than the latency periods of 63.1 days for group 3, given HA before DMBA, and 62.9 days for Group 5, the DMBA only group. The incidence of tumors at the end of the experiment did not differ significantly. HA caused excessive growth and secretory activity in the mammary gland. Atrophic changes were evident among DMBA treated animals 19 days after DMBA administration. By 5 wk after carcinogen administration the lobules had mostly disappeared. The mammary glands of the rat which received HA for 14 days before DMBA were partially protected against the DMBA induced destruction and contained some areas where the lobules were well preserved. A delayed effect of DMBA treatment was the formation of dark-staining irregular structures which originated either from the larger ducts or from the duct terminals and which were morphologically different from hyperplastic alveolar nodules. (19 refs)

79-5050 Infertility in Mice Following Prenatal Exposure to 9,10-Dimethyl-1,2-benzanthracene (DMBA) (Meeting Abstract). (Eng) MacKenzie, K. M. (Raltech Scientific Services, Incorporated, Madison, WI); Lucier, G. W. *Biol Reprod* 20(Suppl 1): 30A; 1979 (no refs)

79-5051 Effect of Ovariectomy, Adrenalectomy and Hypophysectomy on Carcinogenesis of the Endometrium by 7,12-Dimethylbenz[a]anthracene in Rats. (Eng) Sekiya, S. (Dept. Obstetrics and Gynecology, Chiba Univ. Sch. Medicine, Inohana 1-8-1, Chiba 280, Japan); Kikuchi, Y.; Katoh, T.; Kobayashi, W.; Takeda, B.; Takamizawa, H. *Gynecol Oncol* 7(3): 281-287; 1979.

The effects of ovariectomy (ovx), adrenalectomy (adx), or hypophysectomy (hypox) (performed at 5 wk of age) on endometrial carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA)-impregnated sutures applied to the endometrial cavity were studied using female Sprague-Dawley rats. At 6 wk after DMBA treatment, squamous metaplasia of the endometrial epithelium was frequently found in all but hypox rats. At 12 wk, hyperplasia of squamous-type cells was observed in 2/7 unoperated controls, 1/3 adx rats, and 1/4 ovx rats. At 24 wk, adenocarcinomas were found in 2/10 controls; squamous cell carcinomas were found in 3/10 controls and 1/4 adx rats; and sarcoma was observed in 1/6 ovx rats. No endometrial hyperplasia or carcinoma was observed in any hypox rat. Serum estrone and estradiol values were lower in ovx and hypox rats at 12 and 24 wk than in control and adx rats ($p < 0.02$). Serum progesterone levels were 7.2, 10.3,

2.0, and 0.4 nanograms/ml in the control, adx, ovx, and hypox rats, respectively. The results suggest that endogenous estrogen may play an essential role in chemically-induced endometrial carcinogenesis. (16 refs)

79-5052 Influence of Surface Lipids on Skin Carcinogenesis in Rats. (Eng) Arffmann, E. (Dept. Pathology, Aalborg Hosp. North, P.O. Box 561, DK-9100 Aalborg, Denmark); Hjerne, N. *Acta Pathol Microbiol Scand [A]* 87(3): 143-149; 1979.

The effect of skin-surface lipid extraction (SSLE) on skin carcinogenesis by various carcinogenic hydrocarbons was studied using female Wistar specific-pathogen-free rats. The rats, some of which had undergone SSLE, received 20 topical applications of hydrocarbon at 2-wk intervals. Dibenz(a,h)anthracene (DBA) induced a basalioma in 1/20 rats. 3-Methylcholanthrene (MCA) induced basaliomas in 14/20 rats and a pure squamous cell carcinoma in 1/20. 7,12-Dimethylbenz(a)anthracene (DMBA) induced advanced squamous cell carcinomas, often keratinizing, in 12/20 animals, papillomas in 3/20, and skin sarcomas in 2/20. Benzo(a)pyrene (BP) induced squamous cell tumors with cellular atypia in 8/20 rats, basaliomas in 4/20, and a benign squamous cell papilloma in 1/20. SSLE had no significant effect on tumor type but did increase the latency period and decrease the rate of tumor development in BP- and MCA-treated animals. In contrast, SSLE enhanced the rate of tumor production by DMBA and reduced the latency period. Malignant tumors in sites other than the skin were rarely seen and only in animals treated with DMBA. (17 refs)

79-5053 Differential Susceptibility of the Axilla and Groin of the Mouse to Chemical Oncogenesis. (Eng) Prehn, R. T. (Jackson Lab., Bar Harbor, ME 04609); Karnik, V. *Nature* 279(5712): 431-433; 1979.

The induction of sc sarcomas in the axillary and inguinal regions of female BALB/cByJ and (C57BL/6JN1cr x BALB/cAnN1cr)F₁ mice by implantation of 3-methylcholanthrene (MC)-impregnated wafers was studied. When the concentration of MC in the disks was $\geq 0.5\%$, tumors usually appeared first by the axillary disks. This tendency diminished as the MC concentration was reduced, disappearing at a concentration of 0.01%. Axillary preference also appeared to persist in irradiated-thymectomized mice treated with sc MC. The possibility that the preference was in some way related to immunologic phenomena cannot be discarded, but most of the effect of MC concentration was probably mediated by some nonimmunologic gradient, the effect of which may have been magnified by an altered immune response. (15 refs)

- 79-5054 Tumour-related Antigen Specificities Associated with 3-Methylcholanthrene-treated Rat Embryo Cells. (Eng) Embleton, M. J. (Cancer Res. Campaign Labs., Univ. Nottingham, Nottingham NG7 2RD, England); Baldwin, R. W. *Int J Cancer* 23(6): 840-845; 1979.

Male inbred WAB/Not rats were immunized with syngeneic embryo cells treated in vitro for 18 hr with 10 μ g/ml 3-methylcholanthrene. (3-MC), and their sera were screened for membrane immunofluorescence reactivity against panels of established chemically induced syngeneic rat tumors. Three separate antiserum pools raised against 3-MC-treated cells reacted with certain chemically induced tumors, whereas antisera to control (dimethyl sulfoxide-treated) cells were completely negative. The reactions observed were reproducible and highly specific for particular target tumors. Absorption studies indicated that each antiserum contained antibodies to several different antigens present on different tumors. Antiserum prepared against extranuclear membranes from 3-MC-treated cells, rather than intact 3-MC-treated cells, was negative. This suggests that the antibody responses were directed against antigens arising subsequently to 3-MC treatment and injection into syngeneic hosts. It is postulated that carcinogen treatment results in the acquisition of multiple neoantigens among a treated cell population and that these neoantigens represent an early change in a sequence of events leading to malignant transformation. (19 refs)

- 79-5055 Application of Mass Spectrometry to the Analysis of Polycyclic Aromatic Hydrocarbons and Related Compounds in the Environment. (Eng) Sakuma, T. (York Univ., Toronto, Canada). *Diss Abstr Int [B]* 39(11): 5345-5346; 1979 (no refs)

- 79-5056 Optimization of a Fluorimetric Group Detection Method for Polycyclic Aromatic Hydrocarbons on Silica Gel. (Ger) Hellmann, H. (Albert-Schweitzer-Strasse 9, D-5400 Koblenz, W. Germany). *Fresenius Z Anal Chem* 295(5): 388-392; 1979.

An improved fluorimetric method for the detection and determination of six polycyclic aromatic hydrocarbons (fluoranthene, 3,4-benzofluoranthene, 11,12-benzofluoranthene, 3,4-benzopyrene, 1,12-benzperylene, and indeno[1,2,3-cd]pyrene) in drinking water is described. The detection limit of the individual compounds is <0.1 nanogram. (4 refs)

- 79-5057 Xenobiotics and Chemical Carcinogens Induced Acceleration of Microsomal DNA Synthesis. (Rus) Lerman, M. I. (Inst. Biological and Medical Chemistry, Moscow, USSR); Abakumova, O. Iu.;

Kutsenko, N. G.; Podobed, O. V. *Biokhimiia* 44(4): 699-704; 1979.

The hypothesis that the metabolism of microsomal DNA (msDNA) is associated with the xenobiotic system and that typical inducers of this system can affect the synthesis, repair, and degradation of msDNA was tested. C3HA mice (intact or with ascitic hepatoma 22A) were inoculated with phenobarbital (PB: 60 mg/kg), benzo(a)pyrene (BP: 20 mg/kg), methylnitrosourea (MNU: 30 mg/kg), the protein synthesis inhibitors cycloheximide (CH: 0.25 mg/kg) or puromycin (PM: 0.6 mg/kg), and the DNA repair inhibitors hydroxyurea (HU: 2.5 g/kg) or caffeine (2.5 mg/kg). Administration of BP, MNU, and PB to tumor-free mice resulted in a rapid and marked increase of ¹⁴C-thymidine incorporation into msDNA in the liver, but the msDNA synthesis system in the liver of mice with hepatoma 22A was resistant to MNU, CH, and PM. (11 refs)

- 79-5058 The Relationship Between the Biological Activity and Metabolism of the Polycyclic Hydrocarbons in Cultured Fibroblasts From Various Mammalian Species of Widely Differing Life Spans. (Eng) Moore, C. J. (Temple Univ., Philadelphia, PA 19122). *Diss Abstr Int [B]* 39(11): 5339; 1979 (no refs)

- 79-5059 The Use of the *Salmonella*/Microsomal Assay to Determine Mutagenicity in Paired Chemical Mixtures. (Eng) Salamone, M. F. (Centre Res. Environmental Quality, York Univ., 4700 Keele St., Downsview (Toronto), Ontario M3J 2R3, Canada); Heddle, J. A.; Katz, M. *Can J Genet Cytol* 21(1): 101-107; 1979.

The mutagenicities of two sets of chemicals acting singly and in pairwise combinations were studied in the *Salmonella*/microsomal assay. The first set consisted of the promutagens benzo(a)pyrene (BP) and benzo(rst)pentaphene [B(rst)P]. The second set contained the direct-acting mutagens methylnitronitrosoguanidine (MNNG) and ethyl methanesulfonate (EMS). In the tests with BP and B(rst)P, the quantities of S-9 mix ranged from 0.05 to 1.0 ml with increasing concentrations of each chemical. At any one chemical concentration, there was a quantity of S-9 that produced a max number of revertant colonies in *S. typhimurium* TA98 or TA100. Excess quantities of the mix partially or totally inhibited the mutagenicity of BP or B(rst)P. No additive mutagenic effects were observed when the two chemicals were tested in combination. MNNG or EMS, when tested individually without the S-9 mix, produced almost linear responses with increasing concentration. In combination, these chemicals also showed linear responses that closely approximated the theoretical additivity, indicating that the mutagenicity of the mixtures was the sum of the activities of each component. (12 refs)

79-5060 Biological Activity of Benzo[*a*]pyrene. An Assessment Based on Mutagenic Activities and Metabolic Profiles of the Polycyclic Hydrocarbon and its Derivatives. (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110); Levin, W.; Thakker, D. R.; Yagi, H.; Chang, R. L.; Ryan, D. E.; Thomas, P. E.; Dansette, P. M.; Whittaker, N.; Turujman, S.; Lehr, R. E.; Kumar, S.; Jerina, D. M.; Conney, A. H. *J Biol Chem* 254(11): 4408-4415; 1979.

The mutagenic activity of benzo(e)pyrene (BeP) and six of its derivatives was studied in the absence and presence of a cytochrome P-450-dependent monooxygenase system. In the presence of hepatic microsomes from Aroclor 1254-pretreated rats or the cytochrome P-450-dependent monooxygenase system purified to near homogeneity for these microsomes, BeP, *trans*-9,10-dihydroxy-9,10-dihydro-BeP (bay region dihydrodiol) and *trans*-9,10-dihydroxy-9,10,11,12-tetrahydro-BeP were metabolized to products which had little or no mutagenic activity toward strains TA98 and TA100 of *Salmonella typhimurium*; products formed from *trans*-4,5-dihydroxy-4,5-dihydro-BeP (K-region dihydrodiol) had modest mutagenic activity; and products from 9,10-dihydro-BeP were 10- to 25-fold more active than those from BeP. The high intrinsic mutagenic activity of the chemically synthesized benzo ring tetrahydroepoxide of 9,10-dihydro-BeP in both strains of bacteria and in cultured Chinese hamster V79 cells suggested that the high mutagenicity of 9,10-dihydro-(BeP) after metabolism was mediated by this bay region tetrahydroepoxide. Liver microsomal metabolites of several of the BeP derivatives were analyzed by high pressure liquid chromatography. Results indicated that lack of formation of a benzo ring epoxide from 9,10-dihydroxy-9,10-dihydro-BeP may explain its inability to be metabolically activated by rat liver enzymes to mutagenic products and may contribute to the low carcinogenic activity of benzo(e)pyrene in rodents. (42 refs)

79-5061 Comparative Studies on the Covalent Binding of the Carcinogen Benzo(a)pyrene to DNA in Various Model Systems. (Eng) Jaggi, W. (Inst. Toxicology, Federal Inst. Technology, Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); Lutz, W. K.; Schlatter, C. *Experientia* 35(5): 631-632; 1979.

The covalent binding of tritiated benzo(a)pyrene (BP) was studied in rat liver in vivo, rat liver perfused in situ, single liver cells, liver homogenate, liver microsomes, fibroblasts from a rat granuloma pouch, and cells from rabbit cornea and monkey kidney cell lines. The binding of BP per mg of single liver cell DNA showed remarkably little variability and high specificity. The single cell system represented a valuable compromise between the in vivo system and the microsomal incubation with respect to sensitivity, reproducibility, and biological relevance. The various

model systems differed by a factor of approx 30 with respect to the limit of detection, the single liver cells being only five-fold less sensitive than the microsomal system. Preference would generally be given to the in vivo system, but single liver cells would be recommended if the amount of available radioactivity were a limiting factor, and the liver microsomal system would be recommended for structural analyses of DNA-bound compounds. (12 refs)

79-5062 The In Vitro Metabolism and Covalent Binding of Benzo[*a*]pyrene to DNA Catalysed by Trout Liver Microsomes. (Eng) Ahokas, J. T. (Clinical Pharmacology Unit, Dept. Medicine, Princess Alexandra Hosp., Ipswich Road, Brisbane, Queensland 4102, Australia); Saarni, H.; Nebert, D. W.; Pelkonen, O. *Chem Biol Interact* 25(1): 103-111; 1979.

The production of reactive intermediates of benzo(a)pyrene (BP) by trout (*Salmo trutta lacustris*), roach (*Rutilus rutilus*), and rat (male Sprague-Dawley) liver microsomes was studied. The binding of BP metabolites to DNA catalyzed by trout liver microsomes was three- to fourfold higher than that catalyzed by rat liver microsomes, although pretreatment of the rats with 3-methylcholanthrene (MC, 25 mg/kg, ip) increased DNA binding thirtyfold. Roach liver microsomes were very inefficient in catalyzing BP binding to DNA. The major nucleoside-metabolite complexes formed by trout and rat liver microsomes from BP were nucleoside adducts of the BP-7,8-diol-9,10-epoxides and the adduct of 9-OH-BP-4,5-oxide. Other products produced by the trout microsomes were the nucleoside adduct of BP-4,5-oxide and nucleoside adducts of BP quinones and/or BP-7,8-oxide. Very little BP-4,5-dihydrodiol was produced by the trout liver microsomes. (36 refs)

79-5063 Formation of Benzo(a)pyrene Metabolite-Nucleoside Adducts in Isolated Perfused Rat and Mouse Liver and in Mouse Lung Slices. (Eng) Kahl, G. F. (Dept. Pharmacology, Univ. Mainz, Mainz, W. Germany); Klaus, E.; Legraverend, C.; Nebert, D. W.; Pelkonen, O. *Biochem Pharmacol* 28(7): 1051-1056; 1979.

The formation of DNA- and RNA-containing adducts with benzo(a)pyrene (BP) metabolites in perfused livers from rats and from mice that are genetically responsive to inducers of cytochrome P₁-450 is described, along with the formation of adducts in lung slices from these mice. The adducts were identified by Sephadex LH20 chromatography. In livers from β -naphthoflavone-pretreated Sprague-Dawley rats, four different deoxyribonucleoside complexes were observed. These were tentatively attributed to DNA modification by the 7,8-diol-9,10-epoxide(s), secondary metabolites of BP quinones, the 4,5-oxide, and secondary metabolites of BP phenols. The diol epoxide-deoxyribo-

nucleoside adducts were also detected in perfused liver and in lung slices from 3-methylcholanthrene-treated genetically responsive C57BL/6N mice, but no adducts were detectable in similar samples from 3-methylcholanthrene-treated genetically nonresponsive DBA/2N mice. In the perfused liver of phenobarbital-pretreated rats, the 4,5-oxide-deoxyribonucleoside adduct was present. These results suggest that some of the BP metabolite-nucleoside complexes generated by microsomes and deproteinized DNA *in vitro* also occur in intact rodent liver and lung tissues. Furthermore, complexes with the diol epoxide(s) were observed with RNA from the perfused liver of β -naphthoflavone-treated, but not from untreated or phenobarbital-treated, rats. Complexes between ribonucleoside(s) and the diol epoxide(s) were also found in perfused liver or lung slices from genetically responsive, but not from genetically nonresponsive mice. (37 refs)

- 79-5064 Induction of Enzyme-altered Islands in Rat Liver by a Single Treatment with Benzo(a)pyrene after Partial Hepatectomy. (Eng) Hirakawa, T. (Dept. Experimental Pathology, Cancer Inst., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan); Ishikawa, T.; Nemoto, N.; Takayama, S.; Kitagawa, T. *Gann* 70(3): 393-394; 1979.

The number of enzyme-altered islands deficient in canalicular ATPase was significantly increased ($p < 0.05$) in the livers of male Sprague-Dawley rats that had received a single ip injection of benzo(a)pyrene (BP: 200 mg/kg) 24 hr following partial hepatectomy. This indicates that BP induces putative precancerous hepatic lesions following partial hepatectomy. The number of enzyme-altered islands was increased even more ($p < 0.02$ in comparison with controls) in hepatectomized, BP-treated rats that received a diet containing 0.05% phenobarbital for 10 wk. (10 refs)

- 79-5065 Binding of 6-Hydroxymethylbenzo(a)pyrene and 6-Acetoxyethylbenzo(a)pyrene to DNA. (Eng) Tay, L. K. (Dept. Pharmacology and Medicine, Univ. Kentucky Coll. Medicine, Lexington, KY 40506); Sydnor, K. L.; Flesher, J. W. *Chem Biol Interact* 25(1): 35-44; 1979.

The carcinogenic hydrocarbons 6-hydroxymethylbenzo(a)pyrene (6-HOCH₂-BP) and 6-acetoxyethylbenzo(a)pyrene (6-AcOCH₂-BP) were examined for their ability to bind to rat and calf thymus DNA. The data indicate that there are no appreciable differences in the amount of binding to the two types of DNA. Nonenzymatic binding of 6-HOCH₂-BP was low (5 μ mol hydrocarbon/mol DNA P) but 6-AcOCH₂-BP was bound to a considerable extent (88.4-97.3 μ mol hydrocarbon/mol DNA P). Nonenzymatic

binding of 6-HOCH₂-BP was greatly increased in the presence of ATP. Binding of 6-HOCH₂-BP in the presence of liver microsomes from untreated rats or from rats pretreated with 3-methylcholanthrene (3-MC) never exceeded 5 μ mol hydrocarbon/mol DNA P. Binding of 6-HOCH₂-BP in the presence of a 3'-phosphoadenosine-5'-phosphosulfate generating system was less than nonenzymatic binding mediated by ATP and was dependent on the presence of ATP rather than ATP and sulfate. Binding was reduced by 50% when ADP was employed in the nonenzymatic reaction and was negligible in the presence of AMP or adenosine, indicating that a diphosphate group is necessary. Incubation of 6-HOCH₂-BP with DNA in the presence of ATP, cytidine triphosphate, guanosine triphosphate, or uridine triphosphate showed that ATP was the most effective mediator of the binding reaction. These observations suggest that 6-HOCH₂-BP is converted to a phosphate ester which, like 6-AcOCH₂-BP, is much more reactive than 6-HOCH₂-BP itself. (18 refs)

- 79-5066 Detection of Mutagenic Polycyclic Aromatic Hydrocarbons in African Smoked Fish. (Eng) Mossanda, K. (Laboratoire d'Analyse des Denrees Alimentaires, Universite de Liege, Boulevard de la Constitution, 151, B 4020 Liege, Belgium); Poncelet, F.; Fouassin, A.; Mercier, M. *Food Cosmet Toxicol* 17(2): 141-143; 1979.

The mutagenicity of six polycyclic aromatic hydrocarbons found in African smoked fish was tested in several *Salmonella typhimurium* strains. In the presence of fortified rat liver postmitochondrial fractions, mutagenic activity was observed with o-phenylenepyrene, coronene, benzo(g,h,i)perylene, and triphenylene in the plate incorporation test, and with fluoranthene in the bacterial fluctuation test. No mutagenic effects of benzo(b)fluoranthene were detected in any of the strains. (14 refs)

- 79-5067 Mutagenicity of Coal Tar Preparations Used in the Treatment of Psoriasis. (Eng) Sapers-tein, M. D. (Anaerobic Bacteriology Res. Lab., V.A. Wadsworth Medical Center, Los Angeles, CA 90073); Wheeler, L. A. *Toxicol Lett* 3(6): 325-329; 1979.

The mutagenicity of four coal tar preparations (Zetar Emulsion, Estar, Lavatar, and Coal Tar Solution USP) used to treat psoriasis was evaluated in the Ames *Salmonella*/microsome mutagenicity test. All the tar products were mutagenic when plated with a liver homogenate and cofactors (S9 mix) on *Salmonella typhimurium* strain TA98. There was a fivefold difference in the mutagenicities of these products when they were compared on the basis of his⁺ revertants per microgram of tar. Zetar Emulsion, which contains whole coal tar, was more mutagenic than

the other preparations, which contain selective extracts or distillates of coal tar. This suggests that some of the processed coal tars used in various psoriasis medications may be less mutagenic than crude coal tar itself. (9 refs)

- 79-5068 The Metabolism of Dieldrin and Two of Its Analogues: The Relationship Between Rates of Microsomal Metabolism and Rates of Excretion of Metabolites in the Male Rat. (Eng) Chipman, J. K. (Dept. Physiology & Biochemistry, The University, Whiteknights, Reading RG6 2AJ, Berks, England); Walker, C. H. *Biochem Pharmacol* 28(8): 1337-1345; 1979.

The hepatic microsomal metabolism rate of dieldrin and two of its analogs, 1,2,3,4,9,9-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-*exo*-7,8,-epoxy-1,4-methanonaphthalene (HCE) and 1,2,3,4,9,9-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4-methanonaphthalene (HEOM), was compared with the rate of excretion of their metabolites. Male Wistar rats fitted with reentrant bile duct cannulas were given [^{14}C]-dieldrin, [^{14}C]-HCE, and [^{14}C]-HEOM (15 mg/kg of each) by ip injection. Bile collections were made without anesthesia, and nearly all ^{14}C excretion occurred by this route. ^{14}C excretion rates were max between 20 and 40 min after dosing, and they were much lower for dieldrin [3.17 nanomoles (nmol)/kg/min] than for HCE or HEOM (204 and 298 nmol/kg/min, respectively). Induction of liver enzymes by treatment with sodium phenobarbitone significantly increased ^{14}C excretion with dieldrin (threefold) but not with HCE. For each compound, the rates of ^{14}C excretion in vivo were compared with the rates of metabolism in vitro by liver microsomes. The pattern of primary metabolism observed in vivo was similar to that found in vitro for both HCE and HEOM. Whereas HCE was metabolized predominantly by microsomal monooxygenase attack, both monooxygenase and epoxide hydratase were important in the degradation of HEOM. The microsomal metabolism of HCE and HEOM by noninduced rat liver microsomes was >100 times greater than that reported for dieldrin using induced rat liver microsomes. When values were expressed in terms of unit body wt, the max microsomal metabolism rates for HCE and HEOM were five to six times greater than the corresponding max rates of biliary excretion of their metabolites in noninduced rats. HCE concentrations were measured in liver microsomes from noninduced rats dosed with the chemical. The rates of hydroxylation by liver microsomes at these concentrations were of the same order as the corresponding rates of biliary excretion for the hydroxylated metabolites. The microsomal hydroxylation rate for HCE increased approx 17-fold in terms of liver wt, after phenobarbitone induction. These results suggest that the metabolism rate can limit the excretion rate of dieldrin metabolites in the male rat. With HCE and HEOM, however, the max metabolism rate is much faster and does not apparently influence the excretion rate. There may be a "threshold metabolic rate"

for these highly liposoluble compounds below which the excretion rate is limited by the metabolism rate. (23 refs)

- 79-5069 Carcinogenic Hydrocarbons Increase the Acceptance of Transfer Ribonucleic Acid for Methionine. (Eng) Hradec, J. (Dept. Biochemistry, Oncological Inst., 180 00 Prague 8, Czechoslovakia); Dusek, Z.; Bahna, L. *Biochem Pharmacol* 28(7): 1157-1161; 1979.

Several carcinogenic and noncarcinogenic polycyclic aromatic hydrocarbons (PAH) were preincubated with a subcellular fraction of Wistar rat liver microsomes. After this preincubation, cytosol was isolated from the mixture and tested for its ability to promote the binding of methionine to endogenous transfer RNA (tRNA). Cytosols from subcellular rat liver preparations treated with carcinogenic PAH significantly enhanced the binding of methionine to endogenous tRNA, and tRNA from the same preparations had an increased acceptance for this amino acid if it was incubated with aminoacyl-tRNA synthetases from normal rat liver or from *Escherichia coli*. Preparations pretreated with noncarcinogenic PAH did not differ from controls in these respects. The activity of methionyl-tRNA synthetase was not enhanced by any of the hydrocarbons tested. Methionyl-tRNA was not stimulated if carcinogenic PAH were added directly to the incubation mixtures containing cytosol or the aminoacyl-tRNA synthetases and tRNA. The active intermediates into which parent carcinogenic PAH are converted by microsomal enzymes apparently modify tRNA and, thus, enhance its acceptance for methionine. (28 refs)

- 79-5070 The Effects of Cortisol on Protein Metabolism and on Transfer Ribonucleic Acid Methylase Activity in Rhabdomyosarcoma of Rats. (Eng) De Loecker, W. (Afdeling Biochemie, Departement Humane Biologie, Faculteit der Geneeskunde, K.U. Leuven, Belgium); De Wever, F.; Leyman, A. M.; Doms, D. *Arch Int Pharmacodyn Ther* 238(2): 333-343; 1979.

The effects of cortisol on protein metabolism were examined in rhabdomyosarcomas experimentally induced in male albino Wistar R rats by a single im injection of 0.028 mg cobalt powder into the adductor muscle of the hind limb. In vivo treatment of tumor-bearing animals with 1 or 10 mg cortisol im resulted in a reduced incorporation of [2- ^{14}C]glycine into the tumor proteins. In vitro application of 0.01-100 μg cortisol to tumor slices equally reduced the amino acid incorporation into the proteins. These inhibitions could not be explained by modifications in protein, RNA, or DNA levels or by changes in the membrane function. Factors inhibiting the amino acid incorporation into tumor proteins could be located in the 105,000 $\times g$ supernatant protein fraction. The tumor transfer RNA methylase activity became markedly inhibited by cortisol treatment. (42 refs)

- 79-5071 The Effect of Ethylnitrosourea on the Activity of NAD-Dependent Glycero-3-Phosphate Dehydrogenase in the Fifth Nerve of Developing Rats and its Relation to Myelination and Tumor Induction. (Ger) Coutelle, R. (Zentralinstitut für Krebsforschung der AdW der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Enke, H. *Arch Geschwulstforsch* 49(1): 6-14; 1979.

The effect of a single dose of ethylnitrosourea (ENU; 85 mg/kg sc), injected at birth, on the activity of NAD-dependent L- α -glycero-3-phosphate dehydrogenase (GPDH) in the trigeminal nerve was studied in male and female inbred albino rats between days 7 and 70 of their lives. In the untreated controls, the enzyme activity rose rapidly between days 7 and 35, after which it remained practically constant, indicative of the conclusion of the myelination process by age 35 days. In the ENU-treated rats, the enzyme activity was significantly lower, reaching the values of the 35-day-old untreated animals only at age 63 days. About 26% of the activity values of the treated animals were below the lower confidence limit of the controls. (24 refs)

- 79-5072 Differential Expression of Components of the Adenylate Cyclase System During Growth of Astrocytoma Cells in Culture. (Eng) Harden, T. K. (Dept. Pharmacology, Univ. North Carolina Sch. Medicine, Chapel Hill, NC); Foster, S. J.; Perkins, J. P. *J Biol Chem* 254(11): 4416-4422; 1979.

The amount of cyclic AMP (cAMP) that accumulates in 1321N1 astrocytoma cells in response to isoproterenol (10 μ M) or prostaglandin E₁ (PGE₁) (10 μ M) varies as a function of time of cells in culture. Under normal culture conditions isoproterenol-stimulated cAMP accumulation increased 3- to 4-fold during the first 2 days following subculture and then declined within 1 wk to the original level. In contrast, PGE₁ responsiveness increased by less than 2-fold. Changes in the responsiveness of intact cells were reflected by similar alterations in isoproterenol- and PGE₁-stimulated adenylate cyclase activity in broken cell preparations. Kinetic analysis of the cAMP degradative capacity of cells during 192 hr in culture indicated that only a small change occurred in the phosphodiesterase activity of the cells. The density of β -adrenergic receptors (moles/mg of protein or moles/cell) as measured by the specific binding of ¹²⁵I-hydroxybenzylpindolol increased markedly during the first 2 days of culture, then declined over the next 6 days. Cells cultured for 2-3 days only did not exhibit a further increase in isoproterenol responsiveness or β -receptor density upon subculture, while these increases were seen upon transfer of cells expressing less than optimal responsiveness (ie, 5- to 9-day old cells). Plating of older cells at high density ($>1 \times 10^5$ cells/cm²) also prevented increases in isoproterenol responsiveness and β -adrenergic receptor density. It is concluded that

changes in responsiveness to catecholamines during growth of astrocytoma cells in culture occur as a result of changes in the number of β -adrenergic receptors per cell, which is optimal in sparse cultures and declines as cell density increases past confluency. (23 refs)

- 79-5073 Microsomal Aryl Hydrocarbon Hydroxylase in Rat Adrenal: Regulation by ACTH but Not by Polycyclic Hydrocarbons. (Eng) Guenther, T. M. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, Bethesda, MD 20014); Nebert, D. W.; Menard, R. H. *Mol Pharmacol* 15(3): 719-728; 1979.

Adrenal aryl hydrocarbon hydroxylase (AHH) activity was further characterized in Sprague-Dawley rats. Total P-450 content is >4 times greater in the rat adrenal cortex mitochondria than in microsomes, but AHH activity is >60 times higher in adrenal cortex microsomes than in mitochondria. The rat adrenal microsomal hydroxylase activity is strongly inhibited by α -naphthoflavone in vitro; progesterone 21-hydroxylase (PH) is not. In rats hypophysectomized for 30 days, AHH decreases to about 6% of control values, but PH falls to about 38% of that in sham-operated control animals. Hypophysectomy causes a striking decrease in an electrophoretic band estimated to be about 57,000 daltons. AHH specific activity and this electrophoretic band are restored to normal levels in adrenal microsomes of hypophysectomized rats that have received exogenous ACTH treatment. AHH in adrenal microsomes is not induced, however, in the hypophysectomized or intact rat by 3-methylcholanthrene or high doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin. These data show that AHH and PH may be associated with different forms of adrenal microsomal P-450. It is of interest that AHH in the adrenal of the untreated rat is similar (in sensitivity to α -naphthoflavone and in the presumed association with the 57,000-dalton apoprotein subunit on electrophoresis) to polycyclic aromatic compound-induced AHH and its associated cytochrome P₁-450 in the rat liver. The regulation of the adrenal hydroxylase by the large polypeptide hormone ACTH and the lack of inducibility by polycyclic aromatic compounds, however, are characteristics distinctly different from those of the P₁-450-associated hepatic enzyme. (40 refs)

- 79-5074 Differential Effects of Antioxidants, Steroids and other Compounds of Benzo(a)pyrene 3-Hydroxylase Activity in Various Tissues of Rat. (Eng) Rahimtula, A. D. (Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland, A1B 3X9 Canada); Zachariah, P. K.; O'Brien, P. J. *Br J Cancer* 40(1): 105-112; 1979.

The response of tissue homogenates prepared from control and 3-methylcholanthrene (3-MC)-treated Sprague-Dawley

CHEMICAL CARCINOGENESIS

rats to antioxidants and sterols was examined. Antioxidants such as butylhydroxyanisole and butylhydroxytoluene inhibited the mixed-function oxidation of benzo(a)pyrene (BP) in several tissues of control and 3-MC-treated rats. The enzyme systems in the liver, kidney, and stomach were much more susceptible to inhibition than those in the lung, adrenals, colon, and small intestine. In all tissues except the stomach, 3-MC treatment led to a decrease in the inhibition of BP 3-hydroxylase activity. It is suggested that antioxidants protect against cancer development by inhibiting the formation of carcinogenic metabolites. Of the various steroids tested, only 17 β -estradiol and estrone were significantly inhibitory in most tissues. Cholesterol increased BP 3-hydroxylase activity in the gastrointestinal tract. (45 refs)

- 79-5075 **Prolactin and 3-Methylcholanthrene Induced Cervical Carcinoma. Effect of Bromocriptine.** (Eng) Forsberg, J. G. (Inst. Anatomy, Univ. Bergen, Arstadvollen 19, N-5000 Bergen, Norway); Breistein, L. S. *Acta Pathol Microbiol Scand [A]* 87(3): 151-156; 1979.

Female mice of the NMRI strain were estrogenized by injection with estradiol for the first five days after birth and ovariectomized at the age of 6-9 wk. One wk later, a cotton thread impregnated with 3-methylcholanthrene was inserted into the uterine cervix. Starting on the day of insertion of the thread, and for an additional 6 days, the females were injected with estradiol (E_2 , 5 μ g), ovine prolactin (P, 5 μ g), or 2-bromo- α -ergokryptine mesylate (bromocriptine, 50 μ g), alone or in different combinations. Controls were injected with vehicles only. The animals were killed 4 or 8 wk after insertion of the thread, and the uterine cervix was serially sectioned. A combined treatment with E_2 and P resulted in an increased incidence of invasive epithelial lesions (epidermoid carcinomas of varying stages of differentiation, and one adenocarcinoma) in the uterine cervix. This incidence was higher than in controls or females injected with either hormone separately. Bromocriptine reduced the incidence of invasions, and this reduction could not be restored to the control level by a simultaneous treatment with E_2 and/or P. Finally, the incidence of invasive lesions in the control group of these estrogenized females was higher than that reported in an earlier study using nonestrogenized females. (11 refs)

- 79-5076 **Gastrinoma Associated with Common Bile Duct Obstruction and the Ectopic Production of ACTH.** (Eng) Kyriakides, G. K. (Dept. Surgery, Univ. Miami Sch. Medicine, P.O. Box 016310, Miami, FL 33101); Silvis, S. E.; Ahmed, M.; Vennes, J. A.; Vogel, S. B. *Am J Surg* 137(6): 800-802; 1979.

A case of adrenocortical hyperfunction due to the ectopic production of ACTH by a gastrin-producing pancreatic

tumor occurred in a 41-yr-old man. Cushing's syndrome preceded the appearance of the overt Zollinger-Ellison syndrome by 2 yr. There is evidence that the pancreatic gastrinoma was the source of the ectopic production of ACTH and, possibly, secretin. (14 refs)

- 79-5077 **Membrane Effects of Tumor Promoters: Stimulation of Sugar Uptake in Mammalian Cell Cultures.** (Eng) Lee, L. S. (Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, 701 W. 168th St., New York, NY 10032); Weinstein, I. B. *J Cell Physiol* 99(3): 451-460; 1979.

The effects of the potent tumor-promoting agent, 12-O-tetradecanoylphorbol-13-acetate (TPA), on sugar transport in human, rat, and murine cells were studied. TPA induced a 12-fold stimulation of 2-deoxy-D-glucose (DG) uptake in confluent 3T3 mouse embryo fibroblasts and a 2.5-fold stimulation in HeLa S3 cells. When a series of macrocyclic diterpenes were assayed, their relative potencies in stimulating DG uptake in 3T3 cells correlated with other known biologic effects of these compounds. On a molar basis, TPA was a much more potent stimulator of DG transport than insulin or epidermal growth factor. In HeLa cells, the ED_{50} value of the TPA effect was 0.2 nanomolar. The increase in DG uptake occurred immediately after the addition of TPA, reached a max at 90 min, persisted for at least 3 hr after the removal of TPA from the medium, and was temperature-dependent. The stimulation was not inhibited by cycloheximide or actinomycin D. As in control cells, DG uptake in TPA-treated cells was inhibited by p-hydroxymercurobenzoate, phloridzin, cytochalasin B, and dexamethasone. Although the precise mechanism is not known, evidence is presented that the TPA stimulation of DG uptake is due to enhanced transport of the sugar rather than to effects on intracellular metabolism. The enhanced transport may be secondary to a more generalized change in membrane structure. (43 refs)

- 79-5078 **Diethylstilbestrol and 11 Derivatives. A Mutagenicity Study with *Salmonella typhimurium*.** (Eng) Glatt, H. R. (Institute Pharmacology, Sect. Biochemical Pharmacology, Univ. Mainz, Mainz, W. Germany); Metzler, M.; Oesch, F. *Mutat Res* 67(2): 113-121; 1979.

Diethylstilbestrol (DES) was tested for mutagenicity in *his-Salmonella typhimurium* strains under 10 different metabolic situations (no exogenous metabolizing system; S9 mix from liver homogenate of rats induced with Aroclor 1254, with or without inhibition of epoxide hydratase; liver and/or kidney S9 mix from control or hamsters treated with Aroclor 1254; horse-radish peroxidase + H_2O_2).

Under none of these conditions did DES give any indication of a mutagenic effect. Furthermore, 11 metabolites and other DES derivatives, 2 of them potent inducers of sister-chromatid exchange in cultured fibroblasts, were not mutagenic in any of the tester strains (*S. typhimurium* TA100, TA98, TA1537, TA1535) in the presence or absence of S9 mix from liver homogenate of rats induced with Aroclor 1254. Thus, one of the few known human carcinogens is very resistant to detection by the mammalian enzyme-mediated *S. typhimurium* mutagenicity assay (Ames test). This is especially remarkable since the metabolizing systems used included: (1) some of very high metabolic activity (S9 mix from liver homogenates of rats and hamsters induced with Aroclor 1254); (2) metabolizing systems from organs susceptible to the carcinogenic activity of DES (hamster kidney); and (3) a mixture of (1) and (2) in case both activities are required for the carcinogenic effect in the whole animal. (23 refs)

- 79-5079 Cytogenetic Effects of Diethylstilbestrol-diphosphate (DES-dp) on Mouse Bone Marrow Monitored by the Micronucleus Test. (Eng) Chrisman, C. L. (Dept. Animal Sciences, Purdue Univ., West Lafayette, IN 47907); Baumgartner, A. P. *Mutat Res* 67(2): 157-160; 1979.

Six doses of diethylstilbestrol diphosphate (DES-dp), ranging from 0.01 to 500 mg/kg, were compared with saline and phosphate buffered saline (negative controls) and two doses (10 and 100 mg/kg) of cyclophosphamide (positive control) in the micronucleus test with 115 ICR mice. DES-dp failed to generate a significant increase in micronucleated polychromatic erythrocytes over negative controls. Cyclophosphamide produced a dose-related increase in micronuclei similar to previously published reports. It is concluded that the micronucleus test does not detect the types of chromosomal changes known to be produced by DES-dp and DES. (21 refs)

- 79-5080 DES-stimulated Increase in Leydig Cell LH Receptors in Mouse Strain Susceptible to Estrogen-induced Testicular Tumors (Meeting Abstract). (Eng) Navickis, R. J. (Dept. Reproductive Medicine, Univ. California, San Diego, CA); Hsueh, A. J. *Biol Reprod* 20(Suppl 1): 57A; 1979 (no refs)

- 79-5081 Preparation of the Radioiodinated Histamine Amide of 4-O-(Carboxypropyl)diethylstilbestrol. (Eng) Johnson, H. J. (Dept. Biochemistry, Univ. Arkansas Coll. Medicine, Little Rock, AR 72201); Cer-

nosek, S. F.; Gutierrez-Cernosek, R. M. *J Labelled Compd Radiopharm* 16(3): 501-506; 1979.

The synthesis of a radioiodinated derivative of diethylstilbestrol (DES) by the mixed anhydride coupling reaction is described. With this method, it is possible to avoid introducing iodine directly into the ring structures. Histamine is labeled by the oxidative Chloramine-T method before it is coupled to 4-O-(carboxypropyl)diethylstilbestrol (I). I is prepared by O-alkylation of DES with ethyl 4-bromobutyrate and alkaline hydrolysis of the ethyl ester. Reaction of I with isobutylchloroformate in dioxane in the presence of tri-n-butylamine gives the mixed anhydride, which is then coupled to ¹²⁵I-histamine to give the ¹²⁵I-histamine amide derivative. This derivative demonstrated immunoreactivity when assayed with an antibody to DES (30% bound at a 1/1,000 dilution of the antiserum), thus making possible a potentially useful iodine-based radioimmunoassay for DES. (4 refs)

- 79-5082 Nutritional and Endocrinological Influences of Graded Levels of Calcium and Diethylstilbestrol upon Bone Density and Kidney Mineralization in Mature Rats (Meeting Abstract). (Eng) Kirkowski, A. C. (Cook Coll., Rutgers Univ., New Brunswick, NJ 08903); Evans, J. L. *J Nutr* 109(6): 33; 1979 (no refs)

- 79-5083 Oestrogen-induced Renal Carcinoma. (Eng) Nissenkorn, I. (Dept. Urology, Beilinson Medical Centre, Petah Tiqva, Israel); Servadio, C.; Avidor, I. *Br J Urol* 51(1): 6-9; 1979.

Two patients (aged 65 and 70 yr) who had been treated for prostatic carcinoma with low-dose diethylstilbestrol (3 mg/day) for 3.5 and 3 yr, respectively, developed renal carcinomas. The first patient was admitted for disturbances in micturition. Physical examination was unremarkable except for slight tenderness over the left loin and a small, firm, nodular prostate. Excretory urogram revealed a non-functioning left kidney. Left retrograde pyelography demonstrated a filling defect in the renal pelvis and a normal ureter. Histological examination of the resected tumor revealed a renal carcinoma penetrating into the calices and renal pelvis. The tumor mass infiltrated the upper ureter and extended through the renal capsule into the perirenal tissue. The second patient was being treated for a pathological fracture of the left femur. Histological examination of a specimen from the fractured femur revealed metastatic renal carcinoma, and excretory urography demonstrated a space-occupying lesion in the left kidney. Distant metastases were found in the thoracic vertebrae in the first patient and in the liver and left femur in the se-

cond. Patients with prostatic carcinoma receiving prolonged estrogen therapy should undergo iv pyelography at regular intervals. (9 refs)

- 79-5084 A Novel Fluorinated Derivative of Diethylstilbestrol. (Eng) McLachlan, J. A. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709); Baucom, K.; Korach, K. S.; Levy, L.; Metzler, M. *Steroids* 33(5): 543-547; 1979.

The synthesis of a diethylstilbestrol (DES) derivative (tetrafluorodiethylstilbestrol, TFDES) with fluorine atoms present in positions ortho to the hydroxyl in each ring is described. TFDES showed extensive oxidation in vitro to the corresponding dienestrol derivative, and at 100 µg/kg, TFDES and DES had comparable in vivo uterotrophic activities. Competitive binding experiments showed that TFDES was 20-25 times less reactive than DES in the mouse uterine estrogen receptor assay. (13 refs)

- 79-5085 Lack of Oestradiol-DNA Binding in Mouse Embryo Cell Cultures or Following Rat-Liver Microsomal Metabolism. (Eng) Duncan, S. J. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Buckinghamshire HP8 4SP, England); Brookes, P. *Cancer Lett* 6(6): 351-355; 1979.

The binding of estradiol-17β to the DNA of mouse embryo cells in culture and to DNA added to a microsomal incubation was examined and compared to the binding of benzo(a)pyrene (BP) to DNA. Primary mouse embryo cell cultures were treated with (³H)BP or (³H)estradiol-17β at a concentration of 0.04 µg/ml of medium. In the microsomal incubation, the (³H)estradiol-17β (5 Ci/mmol) or (³H)BP (133 Ci/mol) were added at a concentration of 100 nmol/ml. The level of BP binding was 1.0-1.5 µmol/mol P compared to 0.01 µmol/mol P for estradiol-17β. When the DNA was isolated from the microsomal incubation by a phenol extraction followed by alcohol precipitation, the binding level of estradiol-17β was similar to that of BP. However, when the DNA was isolated using the conventional procedure to obtain DNA from cells, the apparent level of estradiol-17β binding was reduced by >85% while the BP binding level remained unchanged. The results give no evidence that estradiol-17β is metabolized by a cytochrome-P-448 oxidase system to a molecular species which is capable of covalent binding to DNA. It seems, however, that NADPH-requiring microsomal metabolism of estradiol results in association of the hormone with a DNA containing complex. This might be explained if specific estrogen-binding proteins had an affinity for DNA. (12 refs)

- 79-5086 A Case of Hepatocytic Adenoma Following Estrogen-Progestogen Treatment. Review of the Published Literature. (Fre) Grandjean, J. P. (Polyclinique Sainte Marie-Therese, 10 avenue Franklin-Roosevelt, 69500 Bron, France); Vignal, J.; Seffert, P.; Mestrallet, G.; Beurlet, J.; Quiviger, P. *Ann Chir* 33(5): 361-370; 1979.

A large hepatocytic adenoma was found in a 30-yr-old woman who had intermittently used oral contraceptives for 8 yr. She had taken ethynodiol diacetate and ethinyl estradiol for 39 mo, then again for 30 mo after a 17-mo intermission; recently, she had taken norethisterone acetate and ethinyl estradiol. Surgery was successful. A total of 160 cases have been reported in the literature. Stopping the use of the oral contraceptives seems to prevent recurrences after surgery, but it is not known whether this measure is sufficient to produce regression of these benign tumors. (58 refs)

- 79-5087 Relationship Between the Uterotropic Effects of 17β-Estradiol and P-1496 and Their Ability to Bind to Estrogen Receptors. (Ita) Iacobelli, S. (Istituto di Clinica Ostetrica e Ginecologica, Universita Cattolica del Sacro Cuore, Rome, Italy); Zenobi, R.; Ranelletti, F. O.; Bompiani, A. *Riv Ital Ginecol* 58(3): 175-182; 1979.

The uterotrophic effects of 6-(dihydroxyundecyl)-β-resorcylic acid-μ-lactone (P-1496) and 17β-estradiol (ED) were compared with the capacity of these compounds to bind to uterine estrogen receptors. The uterotrophic activity of P-1496 was 20 times lower than that of ED, and the affinity of P-1496 for estrogen receptor sites was about 1/20 that of ED. P-1496 and ED bound to the same estrogen receptors. (5 refs)

- 79-5088 Oestrogen Therapy and Endometrial Carcinoma (2 Letters to Editor). (Eng) Studd, J. W. (Dept. Obstetrics and Gynaecology, King's Coll. Hosp., London SE5, England); Thom, M.; Patterson, M. *Lancet* 1(8128): 1239; 1979.

Prolonged usage of unopposed estrogen therapy may, in susceptible patients, produce endometrial cancer, but there is good evidence that the addition of progestagen prevents this increased rate of cancer and, also, hyperplasia. There is no evidence that low-dose cyclical estrogen with progestagen is in any way associated with an increased risk of endometrial cancer. Therefore, 7-13 days of a progestagen should be added each month so that the benefits of estrogen may be achieved with no increased risk of endometrial lesions. (7 refs)

79-5089 Tumors of the Liver and Contraception (Meeting Abstract). (Fre) Monrozies, X. (No affiliation given). *J Gynecol Obstet Biol Reprod (Paris)* 8(1): 75; 1979 (no refs)

79-5090 Mutagenicity in Urine of Nurses Handling Cytostatic Drugs (Letter to Editor). (Eng) Falck, K. (Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, SF-00290 Helsinki 29, Finland); Grohn, P.; Sorsa, M.; Vainio, H.; Heinonen, E.; Holsti, L. R. *Lancet* 1(8128): 1250-1251; 1979.

A sensitive screening procedure using *Escherichia coli* strain WP2 uvrA and *Salmonella typhimurium* strains TA98 and TA100 as indicator organisms was used to detect mutagenic activity in the urine of patients on chemotherapy and of nurses administering these drugs. All patients receiving cytostatic drugs exhibited mutagenicity in their urine, as did most of the nurses. The mutagenicity was significantly higher in the patients' urines. (7 refs)

79-5091 The Response of Ataxia Telangiectasia Cells to Bleomycin. (Eng) Lehmann, A. R. (MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England); Stevens, S. *Nucleic Acids Res* 6(5): 1953-1960; 1979.

Cultured fibroblasts from patients with ataxia-telangiectasia (AT) were sensitive to the lethal effects of bleomycin (BM). As with ionizing radiation, no defects were observed in the overall rejoining of the single- or double-stranded breaks produced by BM. However, since only apyrimidinic (and, to a lesser extent, apurinic) sites are produced by BM, it is tentatively suggested that AT cells are unable to rejoin a very small fraction of the total strand breaks. (29 refs)

79-5092 Effects of Trialkyltin Compounds on *Escherichia coli* JE 1011 and Its NS Mutants. (Jpn) Tatsuguchi, K. (Dept. Food Science and Technology, Kyusyu Univ., Fukuoka 812, Japan); Setokuchi, T.; Yamada, J.; Watanabe, T. *Nippon Nogeikagaku Kaishi* 53(3): 81-86; 1979.

Antimicrobial actions of trialkyltin compounds on *Escherichia coli* JE 1011 and its NS mutants were investigated. Triethyltin chloride (TET) revealed similar antimicrobial action on JE 1011 and NS mutants, and tripropyltin chloride (TET) showed more activity on NS mutants than on JE 1011. Tributyltin chloride (TBT) was effective only on NS mutants. The partition coefficients of TET, TPT and TBT [1-octanol/0.05 M sodium phosphate (pH 7.0) buffer system at 20 C] were 2.5, 22 and 49, respec-

tively, indicating that the greater the carbon number in the alkyl chain of a compound, the more hydrophobic it will be. Lipopolysaccharides (LPS) and protein were rapidly released from JE 1011 treated with EDTA. Antimicrobial action on JE 1011 was increased in the case of TPT and TBT by EDTA treatment of the cells, especially in TBT, but not in TET. The results and data on the LPS of these strains suggests that the outer membrane of JE 1011 is a permeability barrier for TPT and TBT, which are more hydrophobic than TET. (20 refs)

79-5093 The Triplet State of 8-Methoxypsoralen. (Eng) Sloper, R. W. (Dept. Chemistry, Paisley Coll., Paisley, PA1 2BE, Scotland); Truscott, T. G.; Land, E. J. *Photochem Photobiol* 29(5): 1025-1029; 1979.

The transient absorption spectra produced by laser flash photolysis of an aqueous soln of 8-methoxypsoralen (8-MOP) were studied. The biphotonic production of hydrated electrons and of the radical ions 8-MOP⁺ and 8-MOP⁻ is reported. The hydrated electron reacted with ground state 8-MOP with k approx $3 \times 10^{10} M^{-1}s^{-1}$. To obtain a true triplet-triplet absorption spectrum, contributions from the radical ions were subtracted from the overall transient absorption. In addition, contributions from the solvated electron (e_{aq}) to the transient spectrum were removed by using N₂O, low laser intensity to minimize photoionization, or by measuring the transient optical density after the electron had decayed. These three methods each produced the same triplet-triplet spectrum that differs in the red region from previously reported spectra. (21 refs)

79-5094 Formation and Identification of Tetra- and Pentachlorobenzo-p-dioxins from Photolysis of Two Isomeric Hexachlorodibenzo-p-dioxins. (Eng) Buser, H. R. (Swiss Federal Res. Station, CH-8820 Wädenswil, Switzerland). *Chemosphere* 8(4): 251-257; 1979.

The formation of tetra- and pentachlorinated dibenzo-p-dioxins (CDD's) from the UV photolysis of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexa-CDD was studied. Both of these compounds also formed smaller amounts of lower chlorinated dioxins. Each of the hexa-CDDs formed three penta-CDD isomers, all with 3:2 substitutions. They also formed one major, two medium-sized, and up to five minor tetra-CDD isomers, most of them with 2:2 chlorine substitutions. In both cases there was a preferential dechlorination of the hexa-CDD's occurring at the lateral positions flanked on both sides by adjacent chlorines. Two of the minor tetra-CDD's from each hexa-CDD possessed 3:1 chlorine substitutions. The main reaction pathways of the photolytic dechlorination of the two hexa-CDD's are illustrated. (8 refs)

79-5095 Stimulation of Iron Absorption by Polychlorinated Aromatic Hydrocarbons. (Eng) Manis, J. (Div. Gastroenterology, Dept. Medicine, State Univ. New York, Downstate Medical Center, Brooklyn, NY 11203); Kim, G. *Am J Physiol* 236(6): E763-E768; 1979.

The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) on iron absorption were investigated in male Sprague-Dawley rats. Rats were given 0.05 ml dioxane with or without TCDD (33 µg/kg) po or ip, and Fe transport was studied in the duodenal loops in vivo after 1-2 days. Transfer of Fe to the blood or carcass was increased 67% and 41%, respectively, by po and ip treatment. In contrast, the first step of Fe absorption, mucosal uptake, increased only 10% after the po dose and not significantly after the ip dose. Thus, the major effect is on Fe transfer from the mucosa into the bloodstream rather than on the Fe uptake from the lumen of the gut. The results were confirmed in studies with everted gut sacs. The effect was max at 1-2 days with a dose of 22-42 µg/kg. Calcium transport was inhibited by TCDD, but galactose and proline transport were unaffected. DDT (200-800 mg/kg in 0.2 ml dioxane, po) also stimulated Fe transport. The stimulation of Fe transport by TCDD was accompanied by an increase in aryl hydrocarbon hydroxylase activity in the intestine and liver. The results suggest that polychlorinated aromatic hydrocarbons may affect the intestinal absorption of essential mineral nutrients. They

also provide further evidence for the two-step mechanism of Fe absorption. (31 refs)

See also:

- *(Rev.): 79-4801, 79-4802, 79-4803, 79-4804, 79-4805, 79-4806, 79-4807, 79-4808, 79-4809, 79-4810, 79-4811, 79-4812, 79-4813, 79-4814, 79-4815, 79-4816, 79-4817, 79-4818, 79-4819, 79-4820, 79-4821, 79-4822, 79-4823, 79-4824, 79-4825, 79-4826, 79-4827, 79-4828, 79-4829, 79-4830, 79-4831, 79-4832, 79-4833, 79-4834, 79-4835, 79-4836, 79-4837, 79-4838, 79-4839, 79-4840, 79-4841, 79-4842, 79-4843, 79-4844, 79-4845, 79-4846, 79-4847, 79-4848, 79-4849, 79-4850, 79-4851, 79-4852, 79-4853, 79-4854, 79-4855, 79-4861, 79-4864, 79-4909, 79-4917, 48-4918, 79-4919, 79-4920, 79-4921, 79-4923, 79-4927, 79-4928, 79-4929, 79-4932.
- *(Phys.): 79-5099, 79-5100, 79-5103, 79-5104.
- *(Viral): 79-5196, 79-5200, 79-5209.
- *(Immun.): 79-5235, 79-5248, 79-5256, 79-5277.
- *(Path.): 79-5309.
- *(Epid.-Biom.): 79-5354, 79-5355, 79-5356, 79-5358, 79-5362, 79-5364, 79-5365, 79-5366, 79-5367, 79-5368, 79-5369, 79-5371, 79-5372, 79-5374, 79-5375, 79-5376, 79-5383, 79-5389.

PHYSICAL CARCINOGENESIS

- 79-5096 Detection of Chromosome Aberrations in B Lymphocytes of Atomic Bomb Survivors. (Jpn) Kamada, N. (Dept. Internal Medicine, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan); Oguma, N.; Tanaka, R.; Pant, G. S.; Kuramoto, A.; Katsuki, T.; Hinuma, Y.; Morita, M.; Abe, T. *Jpn J Clin Hematol* 20(4): 346-354; 1979.

The presence of chromosome aberrations in the B lymphocytes of four atomic bomb survivors was detected by a new method in which the Epstein-Barr virus (EBV) sensitivity of B lymphocytes was used to isolate and culture cells in mitosis. All four subjects (2 women and 2 men aged 15-37 yr at the time of the bomb) had been 550-750 m from the epicenter of the explosion and had received an estimated 200-638 rads. EBV-sensitive B lymphocytes isolated from the peripheral blood lymphocytes of the subjects were initially cultured on soft agar and then transferred to a liquid culture for further growth. When stained and examined under a microscope, the B lymphocytes of 2/4 survivors showed chromosome aberrations. Of the cells that were able to be analyzed, 8/16 cells from the survivor exposed to 638 rads and 3/24 cells from the survivor exposed to 400 rads contained aberrant chromosomes. Chromosome aberrations were also observed in the T lymphocytes and bone marrow cells of all four subjects. The development of acute B-lymphocytic leukemia, B-cell lymphoma, or multiple myeloma may be elucidated by this technique of isolating and culturing B lymphocytes. (22 refs)

- 79-5097 Chromosome Aberrations in B Lymphocytes of Atomic Bomb Survivors. (Eng) Kamada, N. (Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., 1-2-3 Kasumi-cho, Hiroshima 734, Japan); Kuramoto, A.; Katsuki, T.; Hinuma, Y. *Blood* 53(6): 1140-1147; 1979.

A method for detecting chromosome aberrations in B lymphocytes is described that involves stimulation of B lymphocytes with Epstein-Barr virus (EBV) instead of separation of B lymphocytes by rosette formation. The EBV-stimulated lymphocytes were isolated as single colonies in soft agar and transferred to liquid culture for further growth. The EBV-stimulated B lymphocytes of two heavily exposed atomic bomb survivors showed 50% and 12.5% chromosome abnormalities 30 yr after exposure. The former patient seemed to have a karyotypically abnormal clone of B lymphocytes in vivo. The detection method used and the evidence of chromosome aberrations in B lymphocytes a long time after radiation exposure will be useful

and important in elucidating the processes involved in the development of acute lymphocytic leukemia, B-cell lymphoma, and multiple myeloma among high-risk groups having a history of accidental or therapeutic exposure to radiation or radiomimetic drugs. (14 refs)

- 79-5098 Deposition and Accumulation of Plutonium Isotopes in Antarctica. (Eng) Cutter, G. A. (Center Coastal Marine Studies, Univ. California, Santa Cruz, CA 95064); Bruland, K. W.; Risebrough, R. W. *Nature* 279(5714): 628-629; 1979.

Data on the deposition of plutonium isotopes from the atmosphere at Dome C on the high Antarctic plateau are presented. Profiles of Pu activities suggest that almost all the Pu isotopes injected into the atmosphere have now been removed. The activities of both $^{239} + ^{240}\text{Pu}$ and ^{238}Pu deposited during 1976 at Dome C were only 1.4% of the activities deposited during their respective periods of maximum fallout. (17 refs)

- 79-5099 Tumor-Susceptibility Generated in Mice Treated with Subcarcinogenic Doses of 8-Methoxypsoralen and Long-Wave Ultraviolet Light. (Eng) Roberts, L. K. (Radiobiology Lab., Dept. Anatomy, Univ. Utah Medical Center, Salt Lake, UT); Schmitt, M.; Daynes, R. A. *J Invest Dermatol* 72(6): 306-309; 1979.

The effects of acute treatments with short-wave UV light (UVB) or with 8-methoxypsoralen (8-MOP) followed by long-wave UV light (PUVA) on the growth of an sc inoculated, UV-induced regressor tumor (RD 87) were studied in female C3Hf/HeN mice. Mice treated with PUVA were as susceptible to tumor challenge as mice treated with UVB. Treatment with 8-MOP or UVA alone resulted in tumor rejection. The rate of tumor growth was similar in mice treated with UVB and PUVA and greater in animals treated with UVB or PUVA than in those treated with UVA ($p \leq 0.01$). Treatment of PUVA-treated mice with anti-immune-associated antigen [anti-Ia(k)] serum abrogated their ability to support tumor growth, indicating that the tumor-susceptible state in PUVA-treated mice is mediated or influenced by an Ia⁺ suppressor cell. (30 refs)

- 79-5100 Enhancement of Aryl Hydrocarbon Hydroxylase Activity in Cultured Rodent Cells by

PHYSICAL CARCINOGENESIS

X-Irradiation. (Eng) Venkatesan, N. (Div. Hematology-Oncology, Childrens Hosp. Los Angeles, Los Angeles, CA 90027); Alfred, L. J.; Torralba, G.; Benedict, W. F. *Life Sci* 24(9): 797-802; 1979.

The effect of x-irradiation (5,000 rads) on the aryl hydrocarbon hydroxylase (AHH) activity of mouse C3H/10T1/2 CL8 cells, Syrian hamster embryo (SHE) cells, and hamster fibrosarcoma A(T₁) Cl-3 cells was studied. Irradiation alone increased the AHH activity of the fibrosarcoma cells by 225% and 217%, respectively, expressed on the basis of DNA and protein ($p < 0.001$). Irradiation prior to induction by benz(a)anthracene (BA, 5 or 15 $\mu\text{g/ml}$) increased the activity 157% and 154% on the basis of DNA and protein, respectively, over the additive effects of both agents ($p < 0.001$). Irradiation alone increased the AHH activity of SHE cells by 55% expressed per mg of DNA ($0.005 > p > 0.001$), and irradiation plus BA increased the activity 28% over the additive effects of both agents. Irradiation alone increased the AHH activity of the mouse cells by 86% ($p < 0.001$) and irradiation plus BA increased the activity 59% over the additive effects of both agents ($p < 0.001$). A synergistic effect was also seen with mouse cells treated with 300 rads. (22 refs)

79-5101 Sister Chromatid Exchanges in Human Lymphocytes Exposed to Ionizing Radiation during G₀. (Eng) Littlefield, L. G. (Medical and Health Sciences Div., Oak Ridge Associated Universities, Radiation Emergency Assistance Center and Training Site, Oak Ridge, TN 37830); Colyer, S. P.; Joiner, E. E.; DuFrain, R. J. *Radiat Res* 78(3): 514-521; 1979.

Several authors have reported small, but statistically significant, increases in sister chromatid exchanges (SCE's) in mammalian cells exposed to low-linear energy transfer (LET) radiation during culture in the presence of [³H]-thymidine or bromodeoxyuridine (BUdR). To determine whether ionizing radiation also induces lesions in the unsubstituted DNA of G₀ lymphocytes that lead to SCE's in second division metaphases, human lymphocytes were exposed to 150 or 300 R ⁶⁰Co- γ radiation prior to culture in the presence of phytohemagglutinin and BUdR. Increased frequencies of SCE's were not observed in the irradiated cultures, either in second division metaphases having ring and dicentric chromosomes or those that did not have detectable chromosome aberrations. These findings suggest that SCE frequencies would not be increased in cultured lymphocytes from persons with in vivo exposures to radiation, and they raise questions regarding the efficacy of ionizing radiation in inducing long-lived lesions in native DNA that can subsequently be expressed as SCE's. (30 refs)

79-5102 Fibrosarcoma after Proton-Beam Pituitary Ablation. (Eng) Coppeto, J. R. (1906 N. Main

St., Waterbury, CT 06704); Roberts, M. *Arch Neurol* 36(6): 380-381; 1979.

The occurrence of a brain fibrosarcoma in a 46-yr-old man who had undergone proton-beam ablation of the pituitary 7 yr previously is reported. The first symptoms were headache, loss of libido, polyuria, polydipsia, and constant, painless vertical diplopia. Examination revealed blepharoptosis, in the left eye, mild weakness of the left superior rectus muscle, left-sided anosmia, and acromegalic facies. Biopsy of the floor of the frontal horns 5 mo later suggested glioblastoma multiforme. Soon afterward, horizontal diplopia developed as did bilateral, complete internal and external ophthalmoplegia. The patient died from a pulmonary embolism. There was no evidence of neoplasia outside the central nervous system, but the cavernous sinus and sella were diffusely infiltrated with fibrous tumor which extended forward into the frontal lobes. The tumor was a fibroblastic neoplasm with notable anaplasia and cellular pleomorphism suggestive of malignant fibrous histiocytoma. (10 refs)

79-5103 Acute Myeloid Leukemia During Hodgkin's Disease. (Pol) Dziewulska-Bokiniec, A. (Klinika Radioterapii, Instytut Radiologii i Radioterapii Akademii Medycznej, ul. Debinki 7, 80-211 Gdansk, Poland); Jassem, J. *Acta Haematol Pol* 10(2): 137-140; 1979.

Acute myeloid leukemia developed in a 35-yr-old woman 5 yr after a diagnosis of Hodgkin's disease (HD). She had been treated for the HD with telecobalt radiation (tumor dose 4,500 rads in 5 wk), vinblastine (VLB, 10 mg/wk, 6 iv injections), procarbazine (150 mg/day po for 5 mo), and with the MOPP protocol (VLB, nitrogen mustard, procarbazine, and prednisone; 6 cycles). The leukemogenic effect of intensive radiotherapy and chemotherapy is discussed. (23 refs)

79-5104 Multiple Keratoacanthomas and Squamous Cell Carcinomas Occurring at Psoriatic Treatment Sites. (Eng) Maddin, W. S. (Faculty Medicine, Univ. British Columbia, Vancouver, British Columbia, Canada); Wood, W. S. *J Cutan Pathol* 6(2): 96-100; 1979.

Four cases of psoriasis in which a spectrum of new growths occurred in conjunction with the psoriasis are reported. A 52-yr-old woman developed over 50 new skin lesions beginning 13 yr after the onset of psoriasis. The lesions, which occurred in sites most heavily involved by psoriasis, included benign keratoses, actinic keratosis, in situ squamous cell carcinomas, well-differentiated invasive squamous cell carcinomas, and keratoacanthomas. A 70-yr-old man developed five lesions (including two infiltrating squamous cell carcinomas, an actinic keratosis with in situ squamous

cell carcinoma, and a keratoacanthoma) in areas most heavily involved by psoriasis; the first new lesion appeared 14 yr after psoriasis. A 53-yr-old woman developed multiple keratoacanthomas and squamous cell carcinomas in the areas most heavily involved by psoriasis beginning 36 yr after the appearance of psoriasis. A 53-yr-old man developed a single infiltrating squamous cell carcinoma in a psoriatic plaque 16 yr after the onset of psoriasis. Two of the four patients had deficient immunological responses. It is concluded that multiple treatment measures (topical mediations, systemic immunosuppressive agents, UV light, and grenz rays) may be the main etiologic factor in the production of cutaneous neoplasms in psoriatic patients. (24 refs)

- 79-5105 Basal Cell Epithelioma in a BCG Vaccination Scar (Letter to Editor). (Eng) Nielsen, T. (Odense, Denmark). *Arch Dermatol* 115(6): 678; 1979.

The case report of a 52-yr-old woman in whom basal cell epithelioma and cicatricial stroma occurred in a BCG vaccination scar is presented. The patient had been vaccinated 10 yr before the development of the lesion, in 1968, and she had undergone surgery for a superficial melanoma of the lower part of her left leg during the same year. (5 refs)

- 79-5106 The Disposition of Americium-241 Oxide Following Inhalation by Beagles. (Eng) Craig, D. K. (Biology Dept., Pacific Northwest Lab., Richland, WA 99352); Park, J. F.; Powers, G. J.; Catt, D. L. *Radiat Res* 78(3): 455-473; 1979.

The disposition of americium-241 in beagles was followed for up to 810 days after a single inhalation exposure to $^{241}\text{AmO}_2$ aerosols with an activity median aerodynamic diameter (AMAD) of $1.3\ \mu\text{m}$ and a geometric standard deviation (GSD) of 1.8 for medium (approx 40 nanocurie (nCi)/liter) and high (approx 340 nCi/liter) concentrations. At low concentrations ($<1\ \text{nCi/liter}$), the aerosols were similar (AMAD approx $0.6\ \mu\text{m}$) and the distribution broader (GSD approx 2.6). Excreta were analyzed for up to 30 days postexposure and, when appropriate, during the last week before sacrifice. Tissue analyses for ^{241}Am were conducted on groups of three dogs sacrificed 10, 30, 90, 270, and 810 days postexposure. Forty percent of the final body burden of ^{241}Am was located in tissues other than the lung parenchyma by 10 days postexposure and only 6% remained in the lung by 810 days postexposure. Translocation was primarily to the liver and skeleton, with roughly equal fractions of the final body burden in each at all sacrifice times. There was very little retention in the thoracic lymph nodes ($<1\%$), and ^{241}Am activity in the gonads was negligible ($<0.05\%$) for these dogs. Both the rate of translocation and the organ distribution as a function of time were different from those found in dogs that

inhaled $^{238}\text{PuO}_2$ or $^{239}\text{PuO}_2$. Therefore, data derived from $^{239}\text{PuO}_2$ experiments should not be used to predict the behavior of other transuranic isotopes and elements. (28 refs)

- 79-5107 Tracheal Carcinoma after Tracheostomy. (Eng) Weismann, R. A. (Dept. Surgery, UCLA Sch. Medicine, Los Angeles, CA 90024); Konrad, H. R. *Arch Otolaryngol* 105(6): 364-366; 1979.

The development of tracheal carcinoma in the stoma of a 63-yr-old woman who had worn a tracheostomy tube for 27 yr is reported. The patient began to bleed from the stoma, and a biopsy revealed the presence of invasive, moderate to poorly differentiated, squamous cell carcinoma in the tracheal tissue and stomal skin. One year later, chest x-rays revealed paratracheal and superior mediastinal masses that suggested either direct tumor extension or nodal involvement. The patient remained apparently tumor free after a course of radiation therapy. Trauma appears to be a factor in the development of certain malignant tumors of the trachea. The stoma should be examined regularly in any patient who requires prolonged tracheostomy. (11 refs)

- 79-5108 Endobronchial Polyposis Secondary to Thermal Inhalational Injury. (Eng) Adams, C. (Section Pulmonary Medicine and Plastic Surgery, Foster G. McGaw Hosp., Loyola Univ. Chicago, Maywood, IL 60153); Moisan, T.; Chandrasekhar, A. J.; Warpeha, R. *Chest* 75(5): 643-645; 1979.

The case report of a 28-yr-old man who developed endobronchial polyposis as a delayed complication of thermal respiratory injury incurred during a house fire is presented. Symptoms of chronic cough and hemoptysis required bronchoscopic examination 1 mo after admission. Two months after the initial injury, numerous endobronchial polyps were found in the trachea and throughout the bronchial tree. The symptoms subsequently improved over a 6-mo period while the patient was receiving steroid therapy. As far as is known, this delayed complication of inhalation burn injury has not been reported previously. (9 refs)

- 79-5109 Tumor Formation of Rat Ascites Hepatoma Cells in the Traumatized Brain. (Eng) Kawaguchi, T. (Second Dept. Pathology, Fukushima Medical Coll., 5-75 Sugitsuma-cho, Fukushima 960, Japan); Kitamura, H.; Nakamura, K. *Gann* 70(3): 337-342; 1979.

Factors influencing the enhancing effect of physical brain trauma on the formation of brain metastases were examined in female Donryu rats with induced coagulation necrosis

of the cerebral cortex. The rats were then inoculated iv with one of the six strains of rat ascites hepatoma tested. Three of the tumors (AH7974F, AH66F, and AH13) were in the single-cell state and three (AH272, AH7974, and AH601) contained cellular aggregates. None of the tumors produced brain metastases in rats without brain trauma. However, after traumatization of the brain tissue, tumor metastases formed in the lesion, mainly with the single-cell-type tumors. Of the aggregated tumors, only AH272 produced brain metastases. The brain tissue was most susceptible to the tumor cells 10 min or 7 days after trauma induction. On the other hand, after injection of AH13 or AH7974 cells into the carotid artery of traumatized animals, brain metastases were found with both types of tumor. (20 refs)

- 79-5110 Double Tumours of the Liver Following Intravenous Thorotrast Injection. Patho-anatomical Report on Two Cases. (Eng) Wegener, K. (Pathological Inst., Municipal Hosp. Ludwigshafen/Rh., Bremsersstrasse 79, D-6700 Ludwigshafen/Rh., W. Germany); Leipolz-Angermüller, S. *Virchows Arch [Pathol Anat]* 382(1): 63-71; 1979.

A fully developed form of double tumor of the liver derived from the components of the two germ layers following Thorotrast injection and a possible preliminary stage in this process are reported. A 63-yr-old man who had been given Thorotrast 35 yr earlier was found at autopsy to have infiltrating cholangiocellular carcinoma (CCC) of the liver with atypical proliferations of sinusoidal lining cells and metastases in both lungs and the left adrenal. The sinusoidal changes in this case resembled diffuse hemangioendotheliomatosis. A 47-yr-old woman who had been given Thorotrast 34 yr earlier was found at autopsy to have infiltrating CCC of the liver and a hemangioendothelial sarcoma with reticular spreading of tumor cells. The question of whether hemangioendothelial sarcomas are derived from endothelial cells or Kupffer cells is discussed. The number of reported cases of Thorotrast patients with two liver tumors might be low either because postmortem examinations were not performed or because the patients died before the second tumor became established. (33 refs)

- 79-5111 Gastric Carcinoma after Partial Gastrectomy. (Eng) De Boer, J. (Dept. Medicine, Div. Gastroenterology, Univ. Amsterdam, Wilhelmina Gasthuis, Amsterdam, Netherlands); Huibregtse, K.; Tytgat, G. N. *Tijdschr Gastroenterol* 21(3): 157-166; 1978.

The case records, x-rays, and pathological specimens of 100 randomly selected patients (14 women, 86 men) who developed gastric stump carcinoma (GSC) after partial gastrectomy (Ga-x) were analyzed. Eighty-nine patients had a Billroth II resection, 11 a Billroth I. Indications for

Ga-x were gastric ulcer (24), duodenal ulcer (39), and various benign conditions (37). The mean age at Ga-x was 40, and the mean age at diagnosis of the malignancy was 65. The mean interval from Ga-x to diagnosis of GSC was 25.1 yr. The interval was 22.7 and 24 yr for patients who underwent Ga-x for gastric duodenal ulcers, respectively. The younger the patient at initial Ga-x, the longer the interval until diagnosis of GSC. The clinical symptoms for GSC were anorexia, wt loss (73 patients); nausea, vomiting (36); hematemesis, melena (18); dysphagia (17); pain (7); and no symptoms (2). The mean duration of symptoms was 4.8 mo. There was no preference for blood group A. False-negative results were obtained in 16.7% of the patients examined by x-rays, 6.2% of the patients examined by gastroscopy and biopsy. The GSC was located in the anastomotic region in 60%, in the corpus in 18%, and in the cardia in 21%. Undifferentiated adenocarcinoma (AC) was found in 60.3%, well-differentiated AC in 6.8%, and linitis plastica-type AC in 20.5%. The degree of histological differentiation appeared to be inversely related to survival. Damage of the mucosal barrier by duodenogastric reflux, epithelial irritation at the gastro-intestinal junction, chronic atrophic stump gastritis with anacidity, and nitrosamines are implicated in the etiology of GSC. (11 refs)

- 79-5112 Ureterosigmoidostomy and Carcinoma of the Colon. (Eng) Leadbetter, G. W. (Dept. Urology, Medical Center Hosp. Vermont, Burlington, VT); Zickerman, P.; Pierce, E. *J Urol* 121(6): 732-735; 1979.

Two cases of colon carcinoma associated with previous ureterosigmoidostomy (USS) are reported. A 52-yr-old man underwent USS at age 2 yr and a left nephrectomy at 5 yr. A single colon polyp with a moderately well-differentiated adenocarcinoma infiltrating the stalk and superficial portions of the polyp was found at the site of active urine flow. The arrangement of the adenocarcinoma was reminiscent of colitis cystica profunda. A 31-yr-old man who had undergone USS at age 12 yr and a left nephrectomy 3 yr later had a benign lesion at the site of a functional ureteral implant and a moderately differentiated colloid carcinoma at the site of a nonfunctional ureteral implant. Previously reported tumors at the site of USS included 4 cases of benign colonic polyps, 4 transitional cell carcinomas and 29 adenocarcinomas. It has been estimated that USS patients have about a 5% risk of developing carcinoma of the colon at the implant site within 6-50 yr. The colons of individuals <40-yr-old are less susceptible than those of patients >40-yr-old to tumor development. Urine irritation is suggested as the cause of the carcinomas. (34 refs)

- 79-5113 Colonic Adenocarcinomas in Patients with Ureterosigmoidostomies. (Eng) Labow, S. B.

(29 Barstow Road, Great Neck, NY 11021); Hoexter, B.; Walrath, D. C. *Dis Colon Rectum* 22(3): 157-158; 1979.

Two cases of adenocarcinoma of the sigmoid colon developing at the site of a ureterosigmoidostomy (USS) are reported. A 71-yr-old woman presented with adenocarcinoma 41 yr after USS and a 72-yr-old man presented with adenocarcinoma 17 yr after USS. These cases represent the 31st and 32nd reported cases of colonic adenocarcinoma following USS. The av interval between USS and tumor diagnosis was 22 yr, but the av interval was only 9.8 yr in patients who underwent USS because of bladder carcinoma. The etiology of this complication is unknown. It is strongly recommended that careful follow-up of such patients begin several years after establishment of the USS. (16 refs)

79-5114 Carcinoma of Colon after Ureterocolic Anastomosis. Implantation on Calyceal Mucosa. (Eng) Shapiro, A. (Dept. Urology, General Surgery and Pathology, Hadassah Univ. Hosp., Jerusalem, Israel); Berlatzky, Y.; Pfeffermann, R.; Lijovetzky, G.; Caine, M. *Urology* 13(6): 617-620; 1979.

Mucoid adenocarcinoma of the colon developed in two patients (a 37-yr-old woman and a 36-yr-old man) 19 and 34

yr, respectively, after ureterocolic anastomosis for benign conditions. In one patient, a deposit of the colonic neoplasm was found on the mucosa of an upper calyx in the obstructed kidney. This indicates that tumor seeding can occur in the upper urinary tract. Patients who have undergone ureterocolic anastomosis have a greatly increased risk of developing large bowel neoplasms. When suspected, radiologic examination of the colon using a water-soluble contrast material plus rectosigmoidoscopy or colonoscopy are essential. Because of the serious nature of this complication, the recent tendency to use the large bowel in urinary diversions may be hazardous, especially in young patients with a benign disease. (10 refs)

See also:

*(Rev.): 79-4815, 79-4829, 79-4853, 79-4856, 79-4857, 79-4858, 79-4859, 79-4860, 79-4861, 79-4862, 79-4863, 79-4865.

*(Chem.): 79-4955, 79-4957, 79-4995, 79-5025, 79-5034, 79-5094.

*(Viral): 79-5209.

*(Immun.): 79-5236, 79-5273.

*(Path.): 79-5338.

*(Epid.-Biom.): 79-5359, 79-5363, 79-5385, 79-5390.

VIRAL CARCINOGENESIS

79-5115 In Vitro Synthesis of Infectious DNA Copies of the Rous Sarcoma Virus Genome. (Eng)

Mariage, R. (Departement de Biologie Cellulaire et Moleculaire, Institut de Cancerologie et d'Immunogenetique, Equipe de Recherche No. 148 du CNRS, 14 avenue Paul-Vaillant-Couturier, F-94800 Villejuif, France); Hill, M. *Intervirology* 11(5): 307-313; 1979.

Attempts were made to synthesize full-length continuous DNA transcripts of viral RNA in vitro. Detergent-disrupted virions of the Prague strain of Rous sarcoma virus (subgroup B) synthesized, in an endogenous reaction, an uninformative DNA that sedimented in neutral sucrose gradients from 18.5S to >28S. The specific infectivity of this DNA, as measured by endpoint dilution transfection assays, was rather low, 34 infectious units/ μ g. Many uninformative molecules of subgenomic length were synthesized, perhaps in part from the defective virions contained in the virus stock. The endogenous reaction yielded up to 8.5×10^{-7} infectious units per biologically active input virion; ie, nearly 0.1-1 infectious molecules. The in vitro-synthesized RSV DNA gave rise to both transforming-nondefective and transforming-defective viruses in the transfection assays. An interference assay, in which the DNA was synthesized in Schmidt-Ruppin RSV (subgroup D) virions, showed that the subgroup specificity of the virus produced by the in vitro-synthesized DNA was the same as that of the parent virus. (23 refs)

79-5116 Biosynthesis of an Unglycosylated Envelope Glycoprotein of Rous Sarcoma Virus in the Presence of Tunicamycin. (Eng) Diggelmann, H. (Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland). *J Virol* 30(3): 799-804; 1979.

Tunicamycin (TM), an inhibitor of the synthesis of the core sequence for N-glycosidically linked oligosaccharides, was used in an attempt to detect an unglycosylated envelope glycoprotein of Rous sarcoma virus in infected chick embryo fibroblasts. The infected cells were treated with TM (0.1 μ g/ml) to prevent glycosylation of the precursor (pr92gp) to the two viral envelope glycoproteins gp85 and gp35. Pretreatment of the cells with TM for 4 hr resulted in a 90% reduction of [3 H]mannose incorporation into total cellular glycoproteins, intracellular viral glycoproteins, and released virus particles. Protein synthesis and virus particle formation were not significantly affected by the treatment. A new polypeptide made in the presence of TM was identified by immunoprecipitation of pulse-labeled cell lysates with monospecific anti-gp85 and anti-gp35 sera. This

polypeptide, migrating on sodium dodecyl sulfate-polyacrylamide gels as a molecule of 62,000 daltons (pr62), contained no [3 H]mannose, was labeled with [35 S]methionine and [3 H]arginine, could not be chased into the higher-mol-wt glycosylated form, and contained the same [3 H]arginine tryptic peptides as pr92gp. The unglycosylated pr62 was still detectable 2 hr after the cells were pulse-labeled. The lack of glycosylation of pr62 did not seem to reduce its stability. No clear evidence for the incorporation of this molecule or its cleavage products into viral particles could be obtained. To code for an envelope polypeptide of 62,000 daltons, only about 1,500 nucleotides, or 15% of the total coding capacity of the virus, are needed. (19 refs)

79-5117 Genetic Recombination in Rous Sarcoma Virus: The Genesis of Recombinants and Lack of Evidence for Linkage between *pol*, *env*, and *src* Genes in Three Factor Crosses. (Eng) Wyke, J. A. (Imperial Cancer Research Fund Labs., Lincoln's Inn Fields, London WC2A 3 PX, England); Beamand, J. A. *J Gen Virol* 43(2): 349-364; 1979.

The appearance of virus recombinants at early times in mixed infections was studied to identify details of recombination that might otherwise be obscured to the high frequency of recombination. Two Prague strain Rous sarcoma viruses (RSV) distinguishable by host-range differences in the *env* gene and temperature-sensitive (ts) markers in the *pol* and *src* genes were used: ts LA 29 PR-A, which has a ts defect in *src*, and ts LA 355 PR-C, which has a ts defect in *pol*. The former plates on C/C phenotype chick cells but not on C/A phenotype cells; the latter plates on C/A but not C/C cells. In the first type of cross performed, virus was harvested from dually infected cultures after one cycle of replication to see if the progeny produced before reinfection might indicate the stage of infection at which recombination can occur. More than half the virus yield was of parental phenotypes; unequivocal recombinants were rare (8%) and heterozygotes were relatively frequent (24%-32%). Thus, a significant proportion of recombinant genomes appear to arise by segregation of heterozygous virus particles. The members of reciprocal recombinant pairs were not maintained at the same level in the progeny segregating from a heterozygote; during this segregation, one of the markers for a particular gene in the heterozygote apparently becomes more predominant than the other marker. In the second type of cross, both original parental viruses and recombinant viruses from earlier mixed infections were used in longer-than-one-cycle experiments. The levels of reciprocal recombinants were

more equivalent in the mass progeny population than in the previous experiment's progeny population, indicating that there is no restriction on the formation of certain recombinants in these crosses. Linkage between the *pol*, *env*, and *src* genes was very slight, and the progeny arising from double-crossover events were as common as those arising from single-crossover events. Moreover, crosses between all three genes occur at equivalent levels. These results indicate that (1) the three genes are completely unlinked (recombination frequency over the whole genome length is very high and the low level of total recombinants reflects very incomplete mixing of parental genomes) or (2) the genetic map is circular, and the markers are spaced approximately equidistantly along the genome. It is possible that more than one recombination mechanism exists in avian retroviruses. (36 refs)

- 79-5118 Endogenous Virus Expression in Chicken Lines Maintained at the Regional Poultry Research Laboratory. (Eng) Crittenden, L. B. (Regional Poultry Res. Lab., Agricultural Res., U.S. Dept. Agriculture, Science and Education Admin., 3606 E. Mount Hope Road, E. Lansing, MI 48823); Smith, E. J.; Gulvas, F. A.; Robinson, H. L. *Virology* 95(2): 434-444; 1979.

Chicken lines maintained at the Regional Poultry Research Laboratory (RPRL) and free of exogenous lymphoid leukosis virus (LLV) infection were assayed for the expression of endogenous LLV. Embryos were assayed for the expression of infectious subgroup E LLV's, particulate RNA-directed DNA polymerase, antigens that could serve as envelope antigens for the envelope-defective Bryan Rous sarcoma virus (chick helper factor, chf), and the group-specific antigens of the leukosis-sarcoma virus group (gs). RPRL inbred lines 6₁, 6₂, 7₂, 100, and 15B were similar in endogenous virus expression to the previously characterized Beltsville Agricultural Research Center inbred lines 6, 7, 100, and 15. The expression of endogenous LLV was characterized for the first time in three sublines of RPRL line 15 chickens. Line 15₁ was gs⁺ chf⁺; line 15₁₄, gs⁻ chf⁺; and line 15₁₅, gs⁻ chf⁺. Some 15₁ and 15₁₅ embryos produced infectious subgroup E virus, but all 15₁₄ embryos produced infectious subgroup E virus. Two RPRL noninbred lines were also characterized. Line P was segregated for subgroup E virus production and the gs⁺ chf⁺ phenotype. Line N segregated for subgroup E virus production and the gs⁺ chf⁺ and gs⁻ chf⁺ phenotypes. (29 refs)

- 79-5119 Mapping of the Provirus Deoxyribonucleic Acid in the Chromosomes of Reticuloendotheliosis Virus-transformed Avian Cells (Eng) Franklin, J. A. (Univ. Texas, Austin, TX). *Diss Abstr Int [B]* 39(11): 5238; 1979 (no refs)

- 79-5120 Cellular Transformation by Reticuloendotheliosis Virus. (Eng) Franklin, R. B. (Univ. Texas, Austin, TX). *Diss Abstr Int [B]* 39(11): 5238; 1979 (no refs)

- 79-5121 Genetic Control of Resistance to Marek's Disease. (Eng) Longenecker, B. M. (Dept. Immunology, Univ. Alberta, Edmonton, Alberta, Canada); Gallatin, W. M. *IARC Sci Publ* 24(II): 845-850; 1978.

Various Marek's disease (MD)-resistant and MD-susceptible lines of chickens were challenged with an MD tumor cell line (RPL-1) that is capable of growth both in vivo and in vitro. Birds that possessed the B²¹ allele associated with MD resistance were also resistant to the growth of the RPL-1 tumor following the injection of 10⁴ cells. Chickens that possessed B alleles associated with susceptibility to MD were also very susceptible to the growth of the RPL-1 tumor. The growth of RPL-1 cells can therefore be used as a marker of B²¹-associated resistance to MD. Chickens that differ in susceptibility to MD, due to allelic differences at a non-B genetic locus (or loci), did not differ with respect to their capacity to reject RPL-1 cells. This might indicate that different mechanisms are operative in B-associated vs non-B-associated resistance to MD. In addition, females were more susceptible than males to RPL-1 challenge, and the RPL-1 tumor demonstrated a predilection for growth in the ovary. (15 refs)

- 79-5122 Cytotoxicity of Lymphocytes from Chickens with Marek's Disease (MD) to MD Tumour Cell Lines. (Eng) Dambrine, G. (Institut National de la Recherche Agronomique, Station de Pathologie aviaire, Tours-Nouzilly, France); Coudert, F.; Cauchy, L. *IARC Sci Publ* 24(II): 857-862; 1978.

The effect of Marek's disease virus (MDV) infection and oncogenesis on the cytotoxicity of lymphoid spleen cells for MD tumor cell lines (HPRS-1, HPRS-2, and MSB-1) was studied using day-old white Leghorn chickens. Generally, specific cytotoxicity increased with the ratio of lymphoid to target cells and could reach approx 30% for the high ratios. However, at the ratio of 300:1 the specific lysis did not increase as expected. The three lymphoblastoid cell lines were equally destroyed by lymphocytes from chickens with MD. Injection of glutaraldehyde-treated MSB-1 cells in complete Freund's adjuvant into MDV-infected birds did not enhance the in vitro cytotoxicity of spleen lymphoid cells or impair in vivo tumor development. The specific cytotoxic activity exhibited by lymphocytes from MD-infected chickens against MD lymphoblastoid cell lines appears to be directed against the MD tumor-associated surface antigen. (12 refs)

VIRAL CARCINOGENESIS

79-5123 Density-Gradient Separation of Spleen-Cell Subpopulations from Marek's Disease Virus-infected Chickens. (Eng) Theis, G. A. (Dept. Microbiology, New York Medical Coll., Valhalla, NY). *IARC Sci Publ* 24(11): 851-856; 1978.

Density-gradient separated spleen-cell subpopulations from FP chickens infected with Marek's disease virus (MDV) were studied to test the hypothesis that the primary cause of depressed mitogen responses in MD is a depletion of mitogen-responsive T lymphocytes. After gradient separation of normal chicken spleen cell suspensions (NS), cells of greater density in fractions 5-7 made up 70%-85% of the total number of cells recovered. In chickens with acute disease symptoms, 85% of the cells from birds infected with JM-V lymphoblastic leukemia were found in fraction 4 and 50% of those from birds injected with MDV were recovered in fraction 3 (ie, they were more buoyant). Peak numbers of rosette-forming B cells (RFC) in NS were found in fraction 3, whereas max mitogen-induced blastogenesis was detected in the cells of fraction 5. Fewer RFC were found in cells from JM-V-treated chickens, and marked inhibitory effects of mitogens were noted in the buoyant fractions of JM-V and MDS cells. The data suggest that depressed T-cell reactivity in MDS and JM-V cells results from the selective depletion of mitogen-responsive T-cells. (8 refs)

79-5124 Expression of Marek's Disease Virus in Producer and Non-producer Lymphoblastoid Cell Lines. (Eng) Nazerian, K. (Science and Education Admin., Regional Poultry Res. Lab., U.S. Dept. Agriculture, E. Lansing, MI); Payne, W. S. *IARC Sci Publ* 24(11): 635-638; 1978.

Expression of the Marek's disease virus (MDV) genome was studied in two T-cell-derived lymphoblastoid lines (MSB-1 and RPL-1) established from MD tumors and in a B-cell-derived line (TLT-6855) established from an avian lymphoid leukemia tumor. Continuous in vitro propagation of the producer cell line MSB-1 reduced the number of cells producing MDV-related cellular and membrane antigens and the inducibility of these antigens with 5-iododeoxyuridine (IUDR), but it did not change the oncogenicity of the cells for chickens. In contrast, propagation of the nonproducer cell line RPL-1 did not change the nonproductivity of the cell line, but it decreased the transplantability of the cells. The MD lines were free of replicating avian leukosis/sarcoma viruses (LSV), and all three lines were susceptible to infection with LSV of subgroup A. (6 refs)

79-5125 Studies on Resistance to Marek's Disease Tumorigenesis: Effect of Immune Stimulation, Tumour-Cell Vaccines, and Herpesvirus of Turkeys

on Tumour Immunity. (Eng) Donahoe, J. P. (Ohio State Univ., Columbus, OH); Kleven, S. H.; Eidson, C. S. *IARC Sci Publ* 24(11): 1037-1041; 1978.

The effects of immune stimulation, tumor-cell vaccines, and herpesvirus of turkeys (HVT) on immunity of chickens to Marek's disease (MD) were studied. Inoculation of *Corynebacterium parvum* into MD-susceptible chicks did not enhance delayed hypersensitivity (DH) to tumor cells but increased DH to *C. parvum*. Birds vaccinated with the MSB-1 strain of MD tumor cells had significantly higher DH to tumor cells and a significantly lower incidence of mortality and MD lesions. Bursectomized birds were protected by MSB-1 vaccination. DH indices to MD cells were higher in birds vaccinated with HVT than in unvaccinated birds ($p < 0.1$). Absorption of anti-Marek's associated tumor surface antigen sera with HVT-infected cells caused no change in titer. The data indicate that nonspecific immune stimulation may be harmful to tumor resistance, that immune stimulation specific for tumor cells is beneficial, that cellular immunity is involved, and that HVT vaccination acts to stimulate specific cellular immunity against tumor cells. (8 refs)

79-5126 Neonatal Tumour Induction: The Emerging Immune Surveillance Mechanism and Amphibian Embryo Tumorigenesis. (Eng) Mizell, M. (Lab. Tumor Cell Biology, Tulane Univ., New Orleans, LA); McCue, R.; Charbonnet, L. *IARC Sci Publ* 24(11): 835-844; 1978.

Tumor induction in *Rana pipiens* larvae and froglets after inoculation of Lucke tumor herpesvirus (LTHV) during various developmental stages was studied. More than 50% of the animals inoculated during the three earliest stages [embryonic stage (S 20), larval stage (S 25), and early metamorphic stage (TK IV)] developed tumors. Some animals developed as many as four tumors. The majority of tumors resulting from inoculation of S 20 embryos were of the pronephric type, whereas the majority of the tumors resulting from inoculation of the S 25 and TK IV stages were of the mesonephric type. No tumors were induced when inoculation was delayed until after stage TK IV. At the time of inoculation, none of the early embryo/larvae groups had reached the stage of immunological competence during which IgG is produced. The older group, which developed no tumors, had reached immunological competence before inoculation. The relevance of these findings to tumor induction by Epstein-Barr virus is discussed. (10 refs)

79-5127 Genetics of Xenotropic Virus Expression in Mice. I. Evidence for a Single Locus Regulating Spontaneous Production of Infectious Virus in Crosses Involving NZB/BINJ and 129/J Strains of Mice.

(Eng) Levy, J. A. (Dept. Medicine, Cancer Res. Inst., Univ. California, San Francisco, CA 94143); Joyner, J.; Nayar, K. T.; Kouri, R. E. *J Virol* 30(3): 754-758; 1979.

The extent of infectious xenotropic (X-tropic) virus expression in homogenized splenic tissue from the high-virus-expressing NZB/BINJ mice and the non-virus-expressing 129/J mice and their crosses was examined by genetic analysis. The host range of this virus includes human, rat, mink, and dog cells. The data suggest that a single autosomal "dominantlike" gene controls the spontaneous production and release of infectious X-tropic virus in NZB mice. Analysis of infectious virus production in second-backcross families [(F₁ x 129) x 129] confirmed this conclusion. Variations in the amount of X-tropic virus released were evident in all genetic crosses. Virus titers (expressed as focus-forming units per milliliter) of supernatant fluid ranged from high levels in the NZB mice to somewhat lower levels in crosses involving the 129 mice. In the absence of a definite pattern in the titers observed in the genetic crosses studied, the term dominantlike is proposed for the single gene regulating the expression of X-tropic virus in NZB mice. (23 refs)

79-5128 The Effect of Ethidium Bromide on C Type Virus Production and Induction. (Eng) Avery, R. J. (Dept. Biological Sciences, Univ. Warwick, Coventry, CV4 7AL, England); Levy, J. A. *Virology* 95(2): 277-284; 1979.

The effect of ethidium bromide (EB: 0.1-1.0 µg/ml) on the production and induction, by 5-iododeoxyuridine (IUDR), of C-type murine leukemia virus (MuLV) from chronically infected BALB S + L- cells was studied. Production of both spontaneously released and induced virus was suppressed by EB, even at low concentrations. This inhibition was observed when EB was added before, 24 hr after, or together with IUDR, although the most pronounced effects were seen when EB was added before or with IUDR. The effect of EB apparently was not an indirect result of an inhibition of cell growth, and the dye had no substantial effect on cell viability or on the uptake of IUDR. EB lowered the production of infectious virus by a number of cell lines chronically producing a variety of MuLV's. The infectivity of the virus, but not the total production of virus particles or reverse transcriptase, was reduced from 3×10^5 to 3×10^4 focus-forming units/ml. The viability of rat K-NRK cells (producing Kirsten sarcoma and leukemia viruses) was not markedly impaired by EB treatment. (23 refs)

79-5129 An Interferon-sensitive Early Step in the Establishment of Infection of Murine Cells by Murine Sarcoma/Leukaemia Virus. (Eng) Morris, A. G. (Dept. Biological Sciences, Univ. Warwick, Coventry

CV47AL, England); Burke, D. C. *J Gen Virol* 43(part 1): 173-181; 1979.

NIH3T3 mouse cells were infected at very high multiplicity with murine sarcoma/leukemia virus (MSV/MLV) and then cloned. All of the 48 clones obtained were morphologically transformed, all but one showed anchorage-independence of growth, typical of MSV-transformed NIH3T3 cells and most (91%) produced MSV/MLV. When cells pre-treated with 10^4 units/ml of purified interferon (IF) were infected under the same conditions and then cloned in the presence of the same amount of IF, only 6/63 clones were morphologically transformed. The remaining clones showed a degree of anchorage-independence typical of the uninfected parental cells and very few (2.4%) produced virus. Furthermore, the MSV genome could not be rescued in any of the 23 clones tested and only 1/10 clones produced tumors. The properties of these clones remained stable over a period of 10 to 20 passages in the absence of interferon. It is concluded that interferon can irreversibly block an early step in the MSV/MLV infectious process. (21 refs)

79-5130 The Friend Virus Genome: Partial Characterization of a Complete DNA Copy. (Eng) Pragnell, I. B. (Beatson Inst. Cancer Res., Wolfson Lab. Molecular Pathology, Garscube Estate, Switchback Rd., Bearsden, Glasgow, G61 1BD, Scotland); Ostertag, W.; Paul, J.; Williamson, R. *J Gen Virol* 43(part 1): 1-14; 1979.

A complementary DNA probe has been prepared from the Friend murine erythroleukemia virus complex released by Friend cells [FV cDNA(D-)] and Friend cells induced to differentiate [FV cDNA(D+)]. Molecular hybridization analysis showed the following: (a) FV cDNA(D+) is close to being a complete copy of the virus genome, and the distribution of sequences is uniform with the distribution in the Friend virus genome. (b) Hybridization of 70S RNA from the cloned helper virus to the total FV cDNA(D+) probe demonstrates that a larger proportion of the cDNA is specific to the transforming spleen focus-forming virus. (c) Hybridization of the probe to normal and transformed cell DNA shows that there are about seven Friend virus-related genes in normal DNA and almost twice this amount in transformed cell DNA; a significant minor proportion (20%) of the cDNA probe anneals only to virus-related sequences in the transformed cell DNA. (d) An analysis of the kinetics of annealing of the cDNA to an excess template RNA shows that the minimum base sequence complexity of the Friend virus complex is 4×10^6 . (e) An analysis of the cross hybridization between FV cDNA(D+) and 60 to 70S RNA isolated from virus released by uninduced and induced cells shows that the genome of the induced and uninduced Friend virus is almost identical. (32 refs)

VIRAL CARCINOGENESIS

- 79-5131 Characterization of a Protein Found in Cells Infected with the Spleen Focus-forming Virus That Shares Immunological Cross-Reactivity with the gp70 Found in Mink Cell Focus-inducing Virus Particles. (Eng) Ruscetti, S. K. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Linemeyer, D.; Feild, J.; Troxler, D.; Scolnick, E. M. *J Virol* 30(3): 787-798; 1979.

An antigen detected in cells infected with spleen focus-forming virus (SFFV) by a radioimmunoassay specific for the gp70's of murine leukemia mink cell focus-inducing (MCF) viruses was characterized in competition radioimmunoassays with limiting dilutions of antibody and in pulse-labeling studies under conditions of antibody excess. Both methods of analysis indicated that the SFFV-encoded antigen is a glycoprotein with a mol wt of approx 52,000 daltons. The gp52 shared immunological reactivity and methionine-containing tryptic peptides with the gp70 of a Friend MCF virus and was expressed on the surface of SFFV-infected cells as well as in the cytoplasm. The gp52 could be detected in fibroblastic cell lines from several species when these cells were infected with SFFV, in several established erythroleukemic cell lines, and in the spleens of mice recently infected with SFFV. Although it shared immunochemical properties with the gp70 of Friend MCF virus, the gp52 could be distinguished from the MCF gp70 (1) by its apparent lack of group and interspecies immunological determinants, compared with MCF virus-derived gp70's; (2) by its failure to be released from cells infected with SFFV or SFFV plus helper virus; (3) by its mol wt; and (4) by tryptic peptide analysis. The results indicate that SFFV codes for an MCF gp70-related gp52 that is apparently no longer a virion structural protein like the MCF gp70 from which it was originally derived. (31 refs)

- 79-5132 Optimal Conditions for Synthesis of Long Complementary DNA Product with Moloney Murine Leukemia Virus. (Eng) Van Beveren, C. (Lab. Physiological Chemistry, Univ. Leiden, 2333 AL Leiden, Netherlands); Goulian, M. *J Virol* 30(3): 951-954; 1979.

The interrelationships between divalent metals, deoxynucleotide triphosphates (dNTP's), and PP_i in determining the properties of the complementary DNA (cDNA) product from the in vitro reverse transcriptase reaction with detergent-treated Moloney murine leukemia virus were studied. In spite of the severalfold greater amount of cDNA product with Mn²⁺ than with Mg²⁺, the net yield of high-mol-wt cDNA was much greater with Mg²⁺ than with Mn²⁺. This held true, as well, for the reactions containing excess dNTP or dNTP plus PP_i, both of which (as has been reported for Mg²⁺) promote synthesis of the high-mol-wt cDNA product. A high total dNTP concentration remained important for a max high-mol-wt product with Mg²⁺, and it was not replaced by simply providing dNTP in excess over Mg²⁺. Under the conditions tested, the addition of PP_i did not further increase the cDNA product size with Mg²⁺

when compared with dNTP in excess over Mg²⁺. The extent of degradation of the RNA template during the incubations was correlated with the size of the cDNA product. (18 refs)

- 79-5133 Multiple Integration Sites for Moloney Murine Leukemia Virus in Productively Infected Mouse Fibroblasts. (Eng) Bacheler, L. T. (Tumor Virology Lab., Salk Inst., San Diego, CA 92112); Fan, H. *J Virol* 30(3): 657-667; 1979.

The integration sites for viral DNA in mouse 3T6 cells infected with Moloney murine leukemia virus (M-MuLV) were studied by restriction endonuclease cleavage of cellular DNA followed by electrophoresis in agarose gels, blot transfer to nitrocellulose, and detection of M-MuLV-related sequences by hybridization with high-specific-activity ³²P-labeled M-MuLV complementary DNA. When *EcoRI* was used to cleave cellular DNA, numerous DNA fragments with sequence homology to M-MuLV were detected in uninfected mouse cell DNA. These endogenous sequences are mouse specific, since they were not detectable in rat cell DNA and they were found to be related to the 38S genomic RNA of M-MuLV. Infected cells contained additional M-MuLV-specific DNA fragments that were not detected in uninfected cells. Different patterns of M-MuLV-specific DNA fragments were detected in each cloned infected line examined. These data suggest that there are multiple sites for the integration of M-MuLV DNA in infected mouse fibroblasts. Cleavage of infected cell DNA with *BamHI*, which cleaves M-MuLV viral DNA at least twice, released the internal *BamHI* B fragment from each infected line, confirming the presence, in each infected cell line, of integrated M-MuLV DNA sequences that retain some features of the sequence organization of unintegrated M-MuLV DNA. (22 refs)

- 79-5134 The Isolation and Preliminary Characterization of Temperature-sensitive Transformation Mutants of Moloney Sarcoma Virus. (Eng) Blair, D. G. (Lab. Viral Carcinogenesis, Building 41, Suite 400, NCI, Bethesda, MD 20205); Hull, M. A.; Finch, E. A. *Virology* 95(2): 303-316; 1979.

The isolation and preliminary characterization of temperature-sensitive (*ts*) transformation mutants of Moloney murine sarcoma virus (MSV) are described. The mutants were isolated from UV-irradiated viral stocks using a selection and screening procedure based on the ability of MSV-transformed normal rat kidney cells to grow in methylcellulose or agar suspension. Mutants isolated by this procedure formed colonies in agar 1,000- to 10,000-fold more efficiently at 34 C than at 39 C. They also exhibited a transformed morphology and elevated hexose transport levels at 34 C, but they were phenotypically normal at 39 C. Both morphology and hexose transport showed transformed-to-normal and normal-to-transformed

conversion within 12-48 hr of a temperature shift from 34 to 39 C and 39 to 34 C, respectively. In contrast, *ts*-transformed cells suspended in agar and incubated at 39 C for 24 hr showed a 90% reduction in colony-forming ability when the plates were returned to 34 C. Superinfection of nonproducer *ts*-transformed cells with leukemia virus resulted in the rescue of *ts* MSV. Rescued supernatants also contained a high proportion (10%) of wild-type (*wt*) MSV. Repeated cloning of *ts* mutants, either as virus or cells, did not significantly affect the proportion of *ts* or *wt* virus rescued. The ability of *ts*-transformed cells to express the transformed phenotype at 39 C could be restored by *wt* MSV superinfection, but not by murine leukemia virus superinfection. (33 refs)

- 79-5135 Type C RNA Virus Proteins: Lack of Binding Specificity to Host Cell Chromosomal DNA In Vitro. (Eng) Miles, K. (Dept. Pathology, Univ. Chicago, Chicago, IL 60637); Schwartz, S. A. *Exp Cell Biol* 47(2): 81-91; 1979.

The C-type virus protein:eukaryote DNA interaction was examined in vitro to determine whether this regulatory mechanism plays a significant role in the control of RNA tumor virus expression in rat cells. Two different DNA-protein reconstitution methods were used. Rauscher murine leukemia virus, purified from chronically infected rat cell cultures, was iodinated in vitro with ¹²⁵I and dissociated in a nondetergent, high-ionic-strength, urea-containing buffer. The chemically separated ¹²⁵I labeled viral polypeptides were reconstituted with purified DNA by affinity column chromatography and by gradient dialysis renaturation. In both instances, no detectable amount of radioactivity specifically bound to double-stranded DNA of any origin. This observation contrasted with the binding behavior of identically prepared and radiolabeled nonhistone chromosomal proteins purified from rat cell nuclei. This finding may rule out, in eukaryote cells, a well-described prokaryotic regulatory mechanism for the control of integrated viral gene expression. (29 refs)

- 79-5136 Potentiation of Leukemogenicity and Infectivity of Rauscher Leukemia Virus by an Enhancing Factor Present in Egg Fluids. (Eng) Gazit, A. (Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ., Ramat-Aviv, Tel-Aviv, Israel); Eylan, E.; Rosen, N.; Samucha, R. *Exp Cell Biol* 47(1): 29-42; 1979.

These studies demonstrate that the resistance of adult mice to Rauscher leukemia virus (RLV) infection is partially counteracted by sequential ip administration of a low-mol-wt enhancing factor from chicken egg fluids. Sequential ip administration of this factor to BALB/c mice infected with RLV significantly stimulated viral replication, as evidenced by elevated viral DNA polymerase levels in mouse sera.

This stimulation of viral replication correlated with an aggravation of viral leukemogenicity that was reflected by an increased splenomegaly response and a reduction of survival time. The in vivo potentiation of RLV replication and leukemogenicity by the enhancing factor was achieved at least partly at the cellular level, since RLV replication was also stimulated in an in vitro system. It is assumed that the stimulatory effect of the enhancing factor on viral replication is connected with its stimulatory effect on cellular DNA synthesis. (26 refs)

- 79-5137 Depression of Rauscher Leukemia Virus Envelope Glycoprotein gp71 Binding by Lymphoid Cells During Leukemogenesis in Mice. (Eng) Fowler, A. K. (Carcinogenesis Intramural Program, NCI Frederick Cancer Res. Center, NIH, Frederick, MD 21701); Reed, C. D.; Riggs, C. W.; Twardzik, D. R.; Weislow, O. S.; Hellman, A. *Infect Immun* 24(3): 647-655; 1979.

The availability of membrane receptors for the 71,000-dalton envelope glycoprotein (gp71) of Rauscher murine leukemia virus on splenic and thymic cells from BALB/c mice during Rauscher murine leukemia virus-induced leukemogenesis was determined by a radiolabeled gp71 binding assay. Shortly after infection, the relative cellular [¹²⁵I]gp71 binding level decreased, first with splenic cells (at days 7-10 after infection) and later with thymic cells (at days 10-20 after infection). The dependency of the reduction of binding on the replication of the inoculated virus was demonstrated by regression analyses using the cellular gp71 binding level as the dependent variable and the infectious virus titer, as well as viral gp71 and p30 levels, of spleens and thymuses from infected mice as independent variables. With each independent variable, the reduction of gp71 binding for both cell types was highly dependent ($p < 0.01$) on the level of virus detected in their respective organ. In the early stages of leukemogenesis, the [¹²⁵I]gp71 binding level declined to approx 20%-30% of control values. During this period, the rate of reduction of binding was very rapid and, in general, was similar for both splenic and thymic cells. Further progression of the disease resulted in little or no further reduction in binding. This technique may be used to monitor host ecotropic virus synthesis and to study cell-surface virus receptor control mechanisms in vivo. (34 refs)

- 79-5138 Fragility of Attenuated Rauscher Leukemia Virus. (Eng) Barbieri-Weill, D. (Laboratoire de culture de tissus, Institut Gustave-Roussy, Villejuif, France); Leibovitch, S. A.; Athan, E.; Emanoil-Ravicovitch, R.; Harel, J. *Intervirology* 11(6): 326-332; 1979.

A previous study showed that attenuated (RCL-) Rauscher leukemia virus (RLV) was 100 times less infectious in vitro

than virulent (RRL+) RLV and that its leukemogenicity was almost abolished. An attempt was made to correlate these differences in biological properties with some biochemical defect of RCL-. After centrifugation, the amount of reverse transcriptase (RT) activity in aged RCL- (collected 18-24 hr after the medium was changed) was only 25%-30% of that in aged RRL+. When each virus was further centrifuged to equilibrium in a sucrose gradient, no more than 10% of the initial RT activity of aged RCL- was found at the density of intact virions (1.14-1.16 g/cm³), and no visible band could be seen in this zone. In contrast, almost all the initial RT activity of aged RRL+ was found in a visible band. The thermal sensitivity of the RT of both viruses was the same. A 60S-70S RNA could be extracted from aged RRL+, but no high-mol-wt RNA was obtained from aged RCL-. The fragility seemed to increase during aging, as both fresh RCL- (collected after 1-6 hr) and fresh RRL+ banded at 1.14 g/cm³, and high-mol-wt RNA could be extracted from fresh RCL-. Molecular hybridization studies showed that 20% of the nucleic acid sequences related to RLV found in the RNA of RRL+-infected cells were missing in the RNA of cells infected with RCL-. Whatever the role of aging, it seems probable that an intrinsic fragility of RCL- is responsible for the attenuation of its infectivity and leukemogenic potency. (18 refs)

- 79-5139 Analysis of Proteins of Mouse Sarcoma Pseudotype Viruses: Type-specific Radioimmunoassays for Ecotropic Virus p30's. (Eng) Kennel, S. J. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Tennant, R. W. *J Virol* 30(3): 729-734; 1979.

A type-specific radioimmunoassay for ecotropic virus p30's was developed to analyze the proteins of murine sarcoma virus pseudotype viruses. The pseudotypes were prepared by the infection of nonproducer cells (A1-2), which were transformed by the Gazdar strain of mouse sarcoma virus, with Gross (N-tropic), WN1802B (B-tropic), or Moloney (NB-tropic) viruses. The respective host range pseudotype sarcoma viruses were defined by their titration characteristics on cells with the appropriate *Fv-1* genotype. Proteins from virus progeny were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Bands present in both the 65,000- and the 10,000- to 20,000-mol-wt regions of the gel distinguished the pseudotype viruses from their respective helpers. Furthermore, two protein bands were noted in the p30 region of murine sarcoma virus (Gross), one corresponding to Gross virus p30 and another of slightly slower mobility. However, since the mobility of the putative sarcoma p30 is nearly identical to that of WN1802B, its presence could not be established by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Type-specific radioimmunoassays for Gross virus p30 and for WN1802B p30 were used to analyze pseudotype preparations, and among several ecotropic viruses tested, only the homologous virus scored in the respective assay. These assays showed that pseudotype viruses contain only

8%-48% helper-specific p30's; the remainder is presumably derived from the sarcoma virus. (18 refs)

- 79-5140 Establishment of Cell Lines from the Wild Rodent *Millardia meltdada* and Tests for Endogenous Virus. (Eng) Sugiyama, H. (Dept. Tumor Viruses, Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suite 565, Japan); Yutsudo, M.; Toyoshima, K.; Yosida, T. H.; Murata, Y. *Gann* 70(3): 297-303; 1979.

Four cell lines were established from the wild rodent *Millardia meltdada*: an untransformed cell line (MM-D), a nonproducer (NP) cell line transformed by murine sarcoma virus (MM-CL4), and two simian virus 40 (SV40)-transformed cell lines (MM-8, MM-663). MM-D was epithelioid and contact-inhibited, whereas MM-CL4, MM-8, and MM-663 were fibroblastic and showed piling-up behavior. No endogenous virus was induced in *Millardia* cell lines by a long-term culture with various inducers. *Millardia* cell DNA had no nucleotide sequence homology with complementary DNA of either murine leukemia virus or rat endogenous virus. (24 refs)

- 79-5141 Characterization of a Defective Pseudotype Particle of Kirsten Sarcoma Virus. (Eng) Myerson, D. (Dept. Molecular Biology, Albert Einstein Coll. Medicine, Bronx, NY 10461); Scheinberg, D.; Klement, V.; Strand, M.; August, J. T. *Virology* 95(2): 536-549; 1979.

The composition of pseudotype particles of Kirsten sarcoma virus (Ki-SV) rescued from normal rat kidney (NRK) cells by superinfection with woolly monkey leukemia virus (WLV) was analyzed. A cell line was isolated that produces a defective pseudotype particle of Ki-SV without detectable infectious helper virus. NRK cells were infected at low multiplicity with a virus stock obtained by the rescue of Ki-SV with WLV. The individual transformed cell foci that resulted were propagated. One was found to produce noninfectious oncovirus particles containing high reverse transcriptase activity. These defective particles contained an active sarcoma genome but no detectable helper virus genome, as cells fused to the particles became transformed but did not show evidence of helper WLV expression. Nevertheless, the NRK cells producing the defective particles contained the complete WLV genome; after prolonged culture, infectious WLV's were released and rapidly spread through the culture. The defect of the noninfectious particle could be attributed to the absence of the viral envelope glycoprotein. Helper virus *env* gene products were not detected in cells producing the defective particle, and these cells did not exhibit interference to superinfection by WLV. The protein composition of the defective particle was unusual. Major proteins were a WLV p28 and a novel

55,000-dalton protein of rodent origin. The latter was not immunologically related to the known rodent C-type virus *gag* or *env* gene products; nevertheless, it was immunoprecipitated by several anti-murine leukemia virus sera, suggesting that a related protein is commonly present in preparations of purified mouse C-type viruses. (42 refs)

- 79-5142 Induction of Lytic Plaques by Murine Leukemia Virus in Murine Sarcoma Virus-transformed Nonproducer Mouse Cells Persistently Infected with Mouse Hepatitis Virus MHV-S. (Eng) Yoshikura, H. (Dept. Genetics, Inst. Medical Science, Univ. Tokyo, PO Takanawa, Tokyo, Japan); Taguchi, F. *Intervirology* 11(2): 69-73; 1979.

The induction of lytic plaques by murine leukemia virus (MuLV) in cultures persistently infected (PI) with mouse hepatitis virus strain S (MHV-S) is reported. Kirsten murine sarcoma virus-transformed, nonproducer BALB3T3 (K-BALB) cells were PI with MHV-S at a multiplicity of infection (MOI) of about 1. The growth rate of these cells (termed MHV-KB) and the culture morphology were hardly affected by the infection. To determine whether there is an interaction between MHV-S and MuLV in the PI cultures, the MHV-KB cells were superinfected with Abelson MuLV at an MOI of 0.1. After 3-4 days, many giant cells appeared in the MuLV-infected cultures, and massive cytolysis finally resulted. The giant cells appeared when MuLV production began. In spite of the cytological changes produced by the MuLV, the MHV-S titers in the medium were similar for MuLV- and mock-infected cultures. If the MuLV inoculum was diluted serially and used to infect MHV-KB cells, plaques consisting of giant cells appeared in proportion to virus dose. When the MuLV-infected cultures were further submitted to the UV XC assay, comparable numbers of XC plaques were obtained. As a control, K-BALB cells were infected with MuLV. No giant cells appeared, and, in the UV XC assay, a significantly higher titer of MuLV was obtained in MHV-KB cells than in K-BALB cells. (19 refs)

- 79-5143 Inhibition of Murine Sarcoma Virus-induced Foci Formation by Cytidine Analogues and Other Drugs Chemotherapeutically Effective in Human Malignancies. (Eng) Wan, C. W. (Ontario Cancer Inst., 500 Sherbourne St., Toronto M4X 1K9, Canada); Mak, T. W. *Intervirology* 11(5): 291-299; 1979.

The antiviral activities of 12 commonly used chemotherapeutic drugs were tested using the Kirsten murine sarcoma virus transformation focus assay. The plating efficiencies of the cells treated with the drugs were monitored simultaneously. Only the cytidine analogs--cyclocytidine, 1- β -D-arabinofuranosylcytosine (ara-C), and azacytidine--showed a selective effect on inhibition of

viral foci over cytotoxicity. With ara-C, an exposure time of 10-30 hr produced the most pronounced effect on the inhibition of foci formation over that of cytotoxicity. (34 refs)

- 79-5144 Murine Sarcoma Viruses Block Corticosteroid-induced Differentiation of Bone Marrow Preadipocytes Associated with Long-Term In Vitro Hemopoiesis. (Eng) Greenberger, J. S. (Joint Center Radiation Therapy, 50 Binney St., Boston, MA 02115); Davisson, P. B.; Gans, P. J. *Virology* 95(2): 317-333; 1979.

The effects of the Harvey, Kirsten, and Moloney strains of murine sarcoma virus (MSV) infection of NIH/Swiss and BALB/c mouse bone marrow preadipocytes on adipocyte differentiation and hemopoiesis were studied. MSV blocked adipocyte differentiation in whole marrow cultures, decreased the numbers of biologically active colony-forming hemopoietic cells, and increased the proliferating adherent cell compartment. The effect on adipocytes was detected earlier than that on hemopoiesis. The individual bone marrow preadipocytes showed a corticosteroid dependence for differentiation in vitro. MSV prevented differentiation of preadipocytes to colony-forming unit adipocytes (CFUa) under conditions which did not inhibit differentiation of granulocyte-macrophage progenitor cells. CFUa at 14 days after MSV infection released RNA type-C virus with host range identical to that of the input virus. An MSV-specific block of both CFUa formation and insulin-dependent differentiation of the 3T3-L1 embryo preadipocyte cell line was also detected by 14 days. (44 refs)

- 79-5145 Cell Surface Expression of the *env* Gene Polyprotein of Dual-tropic Mink Cell Focus-forming Murine Leukemia Virus. (Eng) Famulari, N. G. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Jelalian, K. *J Virol* 30(3): 720-728; 1979.

The virus-host interaction of mink cell focus-forming (MCF 247) murine leukemia virus was studied in mouse and mink fibroblasts to determine whether any unusual features of protein processing exist. Emphasis was placed on the processing of the *env* gene products. Differences were observed in the kinetics of processing of the *env* gene polyprotein of ecotropic, xenotropic, and dual-tropic MCF murine leukemia virus. In pulse-chase experiments, the *env* gene polyprotein of the dual-tropic MCF virus exhibited a marked increase in stability relative to that of the ecotropic or xenotropic virus. A comparison was made of the cell-surface expression of *env* gene products of ecotropic, xenotropic, and dual-tropic MCF murine leukemia virus. Only gp70 was accessible to lactoperoxidase-catalyzed radioiodination of fibroblasts infected by ecotropic or

kenotropic virus, whereas both gp70 and the *env* gene polyprotein were expressed on the surface of dual-tropic MCF virus-infected cells. (35 refs)

79-5146 Nucleotide Sequence of the Self-priming 3' Terminus of the Single-stranded DNA Extracted from the Parvovirus Kilham Rat Virus. (Eng) Salzman, L. A. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014); Fabisch, P. *J Virol* 30(3): 946-950; 1979.

The parvovirus genome is a linear, single-stranded DNA molecule with double-stranded hairpin termini. The 3' terminus can serve in vitro as a self-primer for the synthesis of a double-stranded viral DNA intermediate. A sequence analysis was made of the nucleotides in the 3' terminus of the single-stranded DNA extracted from the autonomous parvovirus Kilham rat virus, and a model is proposed for the secondary structure of the terminus and the in vitro origin of replication for the complementary viral DNA strand. The data do not allow any final conclusions as to the functional role of all parts of the 3' DNA terminus. They do, however, confirm the probability of a highly structured terminal sequence that is capable of folding back on itself and forming a hairpin turn. This hairpin-shaped, double-stranded DNA could serve as the self-primer for initiation of the viral double-stranded replicative intermediate. (21 refs)

79-5147 Biochemical and Immunological Properties of the Reverse Transcriptase Associated with a Hamster Retrovirus. (Eng) Gregerson, D. S. (Dept. Ophthalmology and Visual Science, Yale Univ. Sch. Medicine, New Haven, CT); Russell, P.; Reid, T. W. *J Gen Virol* 43(2): 327-337; 1979.

An RNA-directed DNA polymerase associated with a hamster retrovirus (HaRV) was characterized. The enzyme is similar to other polymerases from mammalian type-C viruses in that it is more active with Mn^{2+} than Mg^{2+} , uses the reverse transcriptase-specific poly(rCm).oligo(dG) template, possesses substantial endogenous polymerase activity, and is strongly inhibited by homologous antisera and moderately inhibited by antisera against other type-C viruses. In contrast to previous reports of polymerases from other hamster viruses, HaRV polymerase is active in endogenous assays and the activity is associated with a 70,000 mol wt polypeptide in highly purified virions and with 70,000- and 85,000 mol wt polypeptides in fresh, unpurified virus. Only one major peak of polymerase activity eluted from 2-(diethylamino)ethanol-cellulose, but the subsequent elution of this peak from phosphocellulose produced two major peaks of polymerase activity. The mol wt of these two peaks were 70,000 and 85,000 by glycerol density-gradient sedimentation. Antigenically, the HaRV

reverse transcriptase and p30 antigen were most closely related to other rodent retrovirus proteins. (21 refs)

79-5148 Characteristics of a Retrovirus Associated with a Hamster Melanoma. (Eng) Russell, P. (Dept. Ophthalmology and Visual Science, Yale Univ. Sch. Medicine, New Haven, CT); Gregerson, D. S.; Albert, D. M.; Reid, T. W. *J Gen Virol* 43(2): 317-326; 1979.

The continuous culture of a hamster melanoma cell line has led to the spontaneous appearance of a retrovirus (HaRV) with typical type-C characteristics. The virus differs from all other known hamster viruses in its ability to transform murine as well as rat and hamster cells with apparent one-hit kinetics. Guinea pig, human and feline cells were not transformed although reverse transcriptase activity was detected in the supernatant from infected human cells. HaRV-transformed hamster embryo cells produced solid tumors (all nonpigmented) in 4/35 animals when injected into hamsters, but HaRV-transformed murine cells produced no tumors in mice. Injection of HaRV alone in hamsters, mice, and rabbits did not induce tumors. HaRV possesses a 70S RNA that dissociates to 35S in dimethyl sulfoxide, and it has a reverse transcriptase that uses the 70S virus RNA as a template. The size, morphology, and density (1.15 g/ml) are similar to other known type-C viruses. Polyacrylamide gel electrophoresis indicated the presence of polypeptides analogous to those found in other type-C viruses. (24 refs)

79-5149 The Interaction Between Herpesvirus and Oncornavirus of Guinea Pigs: In Vitro and In Vivo Studies. (Eng) Fong, C. K. (Virology Lab., Veterans Admin. Hosp., West Haven, CT); Hsiung, G. D. *IARC Sci Publ* 24(11): 981-989; 1978.

Cultured guinea pig embryo cells doubly infected with guinea pig herpeslike virus (GPHLV) and guinea pig oncornavirus (GPOV) contained pseudotype virus particles with an oncornavirus morphology that were coated with GPHLV antigen, as detected by immunoferritin electron microscopy. Infection of Hartley guinea pigs with both GPHLV and GPOV induced lymph node hyperplasia in a higher percentage of animals than infection with either virus alone. In addition, infection of strain 2 guinea pigs with exogenous GPHLV delayed the development of L₂C leukemia in these animals. (13 refs)

79-5150 Multiple Copies of Shope Virus DNA Are Present in Cells of Benign and Malignant Non-Virus-producing Neoplasms. (Eng) Stevens, J. G. (Dept. Microbiology and Immunology, Sch. Medicine, Univ. California at Los Angeles, Los Angeles, CA 90024); Wetts-stein, F. O. *J Virol* 30(3): 891-898; 1979.

Qualitative and quantitative determinations were made of the extent to which the Shope papilloma virus genome is present in non-virus-producing benign and malignant tumors in domestic rabbits was established. With the use of nick-translated radioactive viral DNA purified from productively infected papillomas on cottontail rabbits as a probe, it was found that (1) papillomas, primary carcinomas, and metastatic carcinomas containing 10 to about 100 copies of the viral genome per diploid cell equivalent of DNA and (2) viral DNA is present in detectable amounts in essentially all neoplastic cells. These results are consistent with the suggestion that the continued presence of the viral genome is necessary for the induction and maintenance of malignant as well as benign neoplasms. (29 refs)

- 79-5151 Nature and Distribution of Feline Sarcoma Virus Nucleotide Sequences. (Eng) Frankel, A. E. (Dept. Medicine, Stanford Univ., Stanford, CA 94305); Gilbert, J. H.; Porzig, K. J.; Scolnick, E. M.; Aaronson, S. A. *J Virol* 30(3): 821-827; 1979.

The genomes of three independent isolates of feline sarcoma virus (FeSV), the Snyder-Theilen (ST), Gardner-Arnstein (GA), and McDonough and coworkers (SM) strains, were compared by molecular hybridization techniques. Using complementary DNA's (cDNA's) prepared from two strains, SM- and ST-FeSV, cDNA's were selected by sequential hybridization to FeSV and feline leukemia virus RNA's. These DNA's were shown to be highly related among the three independent sarcoma virus isolates. FeSV-specific cDNA's were prepared by selection for hybridization by the homologous FeSV RNA and against hybridization by feline leukemia virus RNA. Sarcoma virus-specific sequences of SM-FeSV differed from those of the ST- or GA-FeSV strains, whereas ST-FeSV-specific DNA shared extensive sequence homology with GA-FeSV. Molecular hybridization showed that, each set of FeSV-specific sequences was present in normal cat cellular DNA in approx one copy per haploid genome and that it was conserved throughout Felidae. In contrast, FeSV-common sequences were present in multiple DNA copies and were found only in Mediterranean cats. These results are consistent with the concept that each FeSV strain has arisen by a mechanism involving recombination between feline leukemia virus and cat cellular DNA sequences, the latter being represented within the cat genome in a manner analogous to that of a cellular gene. (34 refs)

- 79-5152 Sarcoma Virus-induced Transformation Specific Antigen: Presence of Antibodies in Cats That Were Naturally Exposed to Leukemia Virus. (Eng) Sliski, A. H. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20014); Essex, M. *Virology* 95(2): 581-586; 1979.

A study was conducted to determine how often cats mount an immune response to FOCMA-S, a transformation-specific antigen believed to be encoded by the feline sarcoma virus (FeSV). Healthy cats that were naturally exposed to feline leukemia virus (FeLV) were examined for the presence of antibodies to FOCMA-S. Anti-FOCMA sera obtained from cats that were viremic with FeLV had analogous end point titers whether tested on FeLV-transformed nonproducer mink fibroblasts or cat lymphoma cell lines productively infected with FeLV. These results suggest that FOCMA-S shares at least one major antigenic determinant with FOCMA-L, which is expressed on lymphoma cells. (19 refs)

- 79-5153 On the Etiological Role of Herpesvirus Ovis in Jaagsiekte. (Eng) Verwoerd, D. W. (Molecular Biology Section, Veterinary Res. Inst., Onderstepoort, S. Africa); De Villiers, E. M.; Coetzee, S. *IARC Sci Publ* 24(II): 869-873; 1978.

The involvement of a herpesvirus (JS-3) in the etiology of jaagsiekte in sheep was studied. Neutralizing antibodies against JS-3 were found in 70% of 400 normal sheep, but only 50% of tumor-bearing sheep with jaagsiekte had antibodies against JS-3. The intratracheal injection of line 15.4 tumor cells derived from a sheep with jaagsiekte into newborn lambs resulted in jaagsiekte in 21/42 animals. Injection of tumor cell homogenates led to the disease being transmitted to 2/8 animals. The disease did not develop in animals inoculated with a tumor DNA extract or with JS-3 virus. In one case, the injection of male 15.4 cells into a female lamb resulted in a tumor with a female karyotype. Hybridization studies with JS-3 virus complementary RNA and DNA from 15.4 cells and jaagsiekte-positive and -negative biopsies showed no evidence for the presence of JS-3 virus genomes in any of these cells. Experimental evidence indicates the involvement of a latent viral genome in the etiology of jaagsiekte, but no conclusive evidence implicating herpesvirus ovis has been found. The possibility of a cocarcinogenic role in conjunction with a C-type RNA tumor virus should be investigated. (7 refs)

- 79-5154 Phosphonoformate Inhibition of Visna Virus Replication. (Eng) Sundquist, B. (Dept. Virology, Faculty Veterinary Medicine, Univ. Agricultural Sciences, Biomedical Center, S-751 23 Uppsala, Sweden); Larner, E. *J Virol* 30(3): 847-851; 1979.

Visna virus was used as a model system to study the inhibition of retrovirus replication by phosphonoformate (PFA). PFA inhibited visna virus replication in sheep choroid plexus cells; a 50% reduction in virus yield was obtained by 20 to 80 μ M PFA. [The discrepancy between the two values (20 and 80 μ M) is probably due to fluctuations involved in the end point titration method.] Morphological changes,

such as syncytia formation and cell degeneration, were reversibly prevented by PFA. Cell growth was not significantly affected by exposure to 500 μ M PFA through five passages, but treatment with 2 mM PFA did arrest cell growth after two to three passages. Cell-free reverse transcriptase activity primed with various synthetic template-primers was inhibited about 90% in the presence of 100 μ M PFA. The results of kinetic experiments suggested that reverse transcriptase was utilized early but not late in the infection cycle. A structurally related substance, phosphonoacetate, did not inhibit visna virus multiplication and had no inhibitory effect on reverse transcriptase activity at a concentration of 500 μ M. (14 refs)

- 79-5155 Transcription of the Bovine Parvovirus Genome in Isolated Nuclei. (Eng) Patton, J. T. (Dept. Biology, Virginia Polytechnic Inst., Blacksburg, VA 24061); Stout, E. R.; Bates, R. C. *J Virol* 30(3): 917-922; 1979.

Nondefective bovine parvovirus (BPV) was used to examine the effects of infection on RNA polymerase activities in nuclei isolated from synchronized bovine fetal spleen cells. The relative levels of total RNA polymerase and RNA polymerase I, II, and III activities in nuclei isolated from BPV-infected and mock-infected cells were similar throughout the course of infection. Hybridization of RNA synthesized in isolated nuclei indicated that BPV-specific RNA synthesis began 8-12 hr postinfection and proceeded linearly until at least 20 hr postinfection. By 20 hr postinfection, 5% of the total RNA synthesis in nuclei from infected cells was virus-specific. BPV-specific RNA synthesis was inhibited by 95% in the presence of 0.1 μ g/ml α -amanitin, suggesting that the viral genome is transcribed by cellular RNA polymerase II. (23 refs)

- 79-5156 Hybridization of Bovine Papilloma Virus Type 1 and Type 2 DNA to DNA from Virus-induced Hamster Tumors and Naturally Occurring Equine Tumors. (Eng) Lancaster, W. D. (Div. Otolaryngology, Case Western Reserve Univ., Cleveland, OH 44106); Theilen, G. H.; Olson, C. *Intervirology* 11(4): 227-233; 1979.

DNA's from bovine papilloma virus (BPV)-induced hamster tumors and from equine connective tissue tumors of unknown etiology were examined for BPV DNA sequences by molecular hybridization. DNA from two distinct classes of BPV (type 1 and type 2) was labeled in vitro and used as probes. Analysis of DNA-DNA reassociation kinetics indicated that both virus types were capable of tumor induction in the hamster. DNA isolated from 6/7 equine tumors accelerated the reassociation of the BPV DNA probes. BPV type 1 or type 2 DNA hybridized extensively to DNA from three tumors, but three other tumors

contained DNA sequences to which only a portion of the probes hybridized. Partial hybridization of probe DNAs to tumor DNA suggested the possible existence of a third BPV class. (19 refs)

- 79-5157 The Characterization of Mason-Pfizer Monkey Virus-induced Cell Fusion. (Eng) Chatterjee, S. (Dept. Microbiology, Univ. Alabama in Birmingham, Medical Center, Birmingham, AL 35294); Hunter, E. *Virology* 95(2): 421-433; 1979.

The characteristics and requirements of multinucleate cell (MNC:syncytium) induction by Mason-Pfizer monkey virus (M-PMV) in human and nonhuman primate cells were investigated. MNC induction by this D-type retrovirus showed single-hit kinetics on human foreskin and rhesus monkey fetal lung cells. The peak of syncytium-forming activity in an isopycnic sucrose gradient coincided with the peak of M-PMV virions, as assessed by electron microscopy and analysis of viral polypeptides. Unlike the paramyxoviruses, M-PMV did not induce "early" cell fusion when added in high concentrations to the target cells. Furthermore, MNC formation was max 48 hr postinfection, and the size of the syncytia remained constant after this time. UV irradiation of M-PMV reduced its ability to form syncytia and to replicate with single-hit kinetics, suggesting that a functional viral genome is required for syncytium formation. Proviral DNA synthesis and assembly of virions were not necessary for cell fusion, since the addition of cytosine arabinoside at concentrations that block virus replication had little effect on MNC formation. Moreover both MNC's lacking detectable intracellular virus polypeptides, and groups of individual, nonfused, but brightly staining cells could be observed in immunofluorescence assays at times when MNC formation was max. Cell fusion was inhibited by the addition of cycloheximide during the first 12 hr of infection, suggesting that de novo protein synthesis is required for MNC formation. The possibility that translation of genomic RNA yields a fusion-inducing product is discussed. (32 refs)

- 79-5158 Immunosuppression Reactivates and Disseminates Latent Murine Cytomegalovirus. (Eng) Jordan, M. C. (Div. Infectious Diseases, Dept. Medicine, Univ. California Sch. Medicine, Los Angeles, CA); Shanley, J. D.; Stevens, J. G. *IARC Sci Publ* 24(II): 769-774; 1978.

The reactivation of murine cytomegalovirus (MCMV) by immunosuppressive techniques was studied in C3H mice. By 4 wk after MCMV inoculation (1,000 plaque-forming units sc), virus was detected only in salivary gland tissue. After 21 days of treatment with rabbit antiserum prepared against murine lymphocytes (ALS), 11/24 mice developed active MCMV infection of the salivary glands and 3/12

developed active infection of the spleen. Reactivation of MCMV infection was achieved in virtually all mice by treatment with ALS plus cortisone acetate (125 mg/kg/day, ip). Among immunosuppressed mice, MCMV infection was widespread and viremia was documented. In unmanipulated mice, the virus appeared to be maintained in a latent state. Attempts to transfer MCMV infection by inoculation of uninfected mice with spleen cells from latently infected mice were unsuccessful. (12 refs)

- 79-5159 Lymphocyte Transformation and Interferon Production as Measures of Cellular Immunity in Lymphoma Patients. (Eng) Arvin, A. M. (Div. Infectious Diseases, Stanford Univ. Sch. Medicine, Stanford, CA); Pollard, R. B.; Rasmussen, L. E.; Rand, K. H.; Merigan, T. C. *IARC Sci Publ* 24(II): 745-751; 1978.

Lymphocyte transformation and interferon production to varicella zoster virus (VZV) were evaluated in 45 untreated lymphoma patients, 35 lymphoma patients who had been in remission for at least 2 yr, and 42 normal VZV-immune subjects. Lymphocyte transformation by VZV antigen did not occur in 44% of the treated subjects, 12/35 patients in remission, and 9% of the normal subjects. There was no detectable interferon production to VZV antigen in 32% of the untreated patients and 4.8% of the controls, and the mean interferon production was significantly depressed in the patients in remission. The mean transformation and interferon production in response to herpes simplex virus (HSV) among 34 HS seropositive patients did not differ from that among 51 normal HSV seropositive subjects; similar results were found among HSV seropositive patients in remission. There was no correlation between defective responses to VZV antigen and pathological diagnosis or stage in the untreated group, nor were the responses correlated with splenectomy or mode of treatment in the remission group. Marked suppression of interferon production and an even greater suppression of lymphocyte transformation were observed in 28 patients tested during the first 6 mo of therapy. The data suggest that lymphocyte transformation by VZV antigen appears to be restored with successful treatment of lymphoma in most patients, whereas the capacity to produce interferon in normal titers remains suppressed in some patients for a prolonged period of time. (28 refs)

- 79-5160 DNA of Epstein-Barr Virus. V. Direct Repeats of the Ends of Epstein-Barr Virus DNA. (Eng) Given, D. (Section Infectious Disease, Dept. Medicine, Univ. Chicago, Kovler Viral Oncology Labs., Chicago, IL 60637); Yee, D.; Griem, K.; Kieff, E. *J Virol* 30(3): 852-862; 1979.

To determine whether the terminal DNA of Epstein-Barr virus (EBV) is a direct or inverted repeat, the structures

formed after denaturation and reannealing of the DNA from one terminus and after annealing of lambda exonuclease-treated DNA were examined electron microscopically. (1) No inverted repeats were detected within the *SalI* D or *EcoRI* D terminal fragments of EBV DNA. The absence of "hairpin- or panhandlelike" structures in denatured and partially reannealed preparations of the *SalI* D or *EcoRI* D fragment and the absence of repetitive hairpin- or panhandlelike structures in the free 5' tails of DNA treated with lambda exonuclease indicated that there is no inverted repeat within the 3×10^5 -dalton terminal reiteration. (2) Denatured *SalI* D or *EcoRI* D fragments reannealed to form circles ranging in size from 3×10^5 to 2.5×10^6 daltons, indicating the presence of multiple direct repeats within this terminus. (3) Lambda exonuclease treatment of the DNA extracted from virus that had accumulated in the extracellular fluid resulted in asynchronous digestion of ends and extensive internal digestion, probably a consequence of nicks and gaps in the DNA. Most full-length molecules, after 5 min of lambda exonuclease digestion, annealed to form circles, indicating that there exists a direct repeat at both ends of the DNA. (4) The findings of several circularized molecules with small, largely double-stranded circles at the juncture of the ends indicated that the direct repeat at both ends is directly repeated within each end. Hybridization between the direct repeats at the termini is likely to be the mechanism by which EBV DNA circularizes within infected cells. (28 refs)

- 79-5161 Analysis of the Transformation of Human Lymphocytes by Epstein-Barr Virus. I. Sequential Occurrence from the Virus-determined Nuclear Antigen Synthesis, to Blastogenesis, to DNA Synthesis. (Eng) Takada, K. (Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Japan); Osato, T. *Intervirology* 11(1): 30-39; 1979.

A B-cell population of human cord blood lymphocytes was exposed to the B95-8 strain of Epstein-Barr virus (EBV), and simultaneous observations of immunofluorescence, cellular morphology and autoradiography were carried out in each individual cell. It was evident that EBV-determined nuclear antigen (EBNA) synthesis occurred prior to blastogenic response and DNA synthesis. EBNA-positive cells could be observed as early as 12 hr after infection and reached a maximum of 17% at 24 hr, followed by a plateau for a subsequent 12 hr. The positive cells were seen exclusively as morphologically normal lymphocytes until 18 hr; at 24 hr, blastogenesis became evident, without cell division. DNA synthesis was detected at 36 hr in EBNA-positive blast cells; subsequently, these cells increased rapidly. EBNA synthesis was similarly evident in the presence of cytosine arabinoside (10 or 20 $\mu\text{g/ml}$) but was significantly inhibited by a short-term exposure to cycloheximide (10 or 20 $\mu\text{g/ml}$) immediately after infection. These findings suggest that the early events in EBV-induced transformation of human lymphocytes occur sequentially from EBNA synthesis, to blastogenesis, to DNA

synthesis and that the crucial step in such transformation probably involves protein synthesis occurring in the very early stage of EBV infection. (14 refs)

- 79-5162 Recovery of Epstein-Barr Virus from Non-producer Neonatal Human Lymphoid Cell Transformants. (Eng) Wilson, G. (Dept. Pediatrics, Howard Hughes Medical Inst. Lab., Yale Univ. Sch. Medicine, New Haven, CT 06510); Miller, G. *Virology* 95(2): 351-358; 1979.

Biological evidence concerning the complexity of Epstein-Barr virus (EBV) DNA in nonproducer cells transformed in vitro is presented. Lymphoid cell lines (LCL) were established by infection of two batches of human umbilical cord lymphocytes with low multiplicities of the B95-8 strain of EBV. Three of the 17 lines released minute amounts of transforming virus; the rest did not, and they did not make capsid antigen. However, virus could be regularly recovered by lethal x-irradiation of transformed cells followed by cocultivation of these cells with primary human umbilical cord WBC. By this technique, transforming activity could be identified in 15/17 lines. These data indicate that the nonproducer human neonatal cell transformants established by EBV infection in vitro possess sufficient genetic information to code for the production of biologically active mature virions. X-rays alone failed to cause a detectable increase in the number of cells with capsid antigen or to enhance extracellular virus production. EBV-positive human serum blocked rescue if it was added during the first 2-4 hr after cocultivation, but not thereafter. Transforming virus could be recovered from x-rayed cells that were then immediately lysed by freezing and thawing. These results suggest that recovery of virus following x-ray and cocultivation is not due to activation of the intracellular virus genome. Rather, it is likely that the method detects small numbers of virions that are cell-associated. Although transforming virus could regularly be rescued from lymphoblastoid cell lines resulting from in vitro transformation, attempts to rescue virus from Raji or EBV-converted BJAB cells were unsuccessful. This discrepancy suggests that there are differences in genome complexity or in genome-cell interactions in different types of EBV-transformed cells. (19 refs)

- 79-5163 Antibody-dependent Autologous Lymphocyte Cytotoxicity Against Cells Freshly Transformed by Epstein-Barr Virus. (Eng) Aya, T. (Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Japan); Matsuo, T.; Takada, K.; Osato, T.; Mizuno, F. *IARC Sci Publ* 24(11): 711-719; 1978.

Cytotoxicity against lymphocytes freshly transformed by Epstein-Barr virus (EBV) was studied in an autologous

system by trypan blue exclusion of EBV nuclear antigen (EBNA)-cells and by the ^{51}Cr -release assay. When EBV-transformed lymphocytes were incubated with EBV-positive serum and autologous unfractionated lymphocytes or K-cells from seropositive healthy donors, the transformed cells were significantly damaged. The cytotoxicity against newly produced EBNA-positive lymphocytes was also remarkable when seropositive healthy donor lymphocytes were exposed to EBV, immediately followed by incubation with positive serum. In contrast, EBV-transformed cells incubated with autologous lymphocytes or T-cells alone were not significantly affected. EBV-positive serum alone was also not cytotoxic, regardless of inactivation. These results strongly suggest that antibody-dependent cellular cytotoxicity (ADCC) plays an important role in immunological defense against EBV oncogenesis in healthy humans. However, ADCC was not seen when immunosuppressed patients were examined. (12 refs)

- 79-5164 Surface Glycoprotein Patterns of Human Haematopoietic Cell Lines. (Eng) Gahmberg, C. G. (Univ. Helsinki, Helsinki, Finland); Anderson, L. C.; Nilsson, K. *IARC Sci Publ* 24(11): 649-653; 1978.

A surface-labeling technique was used to obtain the surface glycoprotein (gp) profile of human hematopoietic cell lines. The exposed surface gp's were labeled with tritiated sodium borohydride after treatment with neuraminidase and galactose oxidase. The radioactive gp's were separated on polyacrylamide slab gels and visualized by autoradiography. Epstein-Barr virus-positive and -negative lines were shown to have different and easily distinguishable surface gp patterns. (7 refs)

- 79-5165 EBV-associated Immune Complexes and Recurrent Burkitt's Lymphoma. (Eng) Gunven, P. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden); Klein, G.; Rosen, A.; Mukojima, T. *IARC Sci Publ* 24(11): 875-882; 1978.

Epstein-Barr virus (EBV)-associated immune complexes were studied in four patients with Burkitt's lymphoma recurring after at least 6-mo remission. Three of these patients had a sudden decrease in anti-EBV-associated cell-membrane antigen (MA) prior to relapse. Low pH filtration of the patients' sera significantly increased anti-MA reactivity above that of serum or control IgG from the periods preceeding the fall in titer. When correction for Ig-G concentration differences was possible, this increased the titer differences. In contrast, the relatively highly reactive sera and their derived fractions generally did not differ markedly in anti-MA reactivity. One exception was probably due to an artefact. In another case, the latest serum from a patient showed a higher anti-MA titer in the low pH-filtered sample than in its control, which suggested that

the factor(s) responsible for the increase in titer after filtration of the low-reactive sera were also present in this serum. Findings indicating the presence of immune complexes with MA specificity in prerecurrence sera in BL suggest that the complexes may promote tumor recurrence, rather than being a consequence of tumor growth. (14 refs)

- 79-5166 IgA and Nasopharyngeal Carcinoma. (Eng) Desgranges, C. (International Agency Res. Cancer, Lyon, France); de-The, G. *IARC Sci Publ* 24(II): 883-891; 1978.

Comparison of sera from patients with nasopharyngeal carcinoma (NPC) with those from patients with Burkitt's lymphoma (BL) or cancers of the head and neck showed that anti-Epstein-Barr virus (EBV) early antigen IgA titers were positive (>5) in the NPC patients only, and that anti-EBV viral capsid antigen IgA titers were higher than 1/40 in the NPC patients and much lower in the other patients. Transforming EBV was found in 9% of NPC salivas, 50% of BL salivas, and 67% of infectious mononucleosis salivas, although the nontransforming salivas did contain EBV clusters. IgA was found only in NPC salivas. These secretory IgA could be used as a rapid means of diagnosing NPC. IgA chains (α) were found in the plasmocytes surrounding NPC tumor tissue, whereas the secretory pieces were present in gland cells as well as in the epithelial tumor cells. (9 refs)

- 79-5167 Evaluation of Delayed Hypersensitivity Reactions to Lymphoid Cell Lines and Antibodies to Epstein-Barr Virus. (Eng) Levine, P. H. (NCI, NIH, Bethesda, MD 20014); Ho, J. H.; Nkrumah, F.; Andrese, A. P. *IARC Sci Publ* 24(II): 893-898; 1978.

Delayed hypersensitivity reactions to the nasopharyngeal carcinoma (NPC)-derived lymphoid cell line HKLY-28 and antibodies (ab) to Epstein-Barr virus (EBV) were measured in 60 Chinese patients with NPC, 20 patients with other carcinomas, and 27 patients with Burkitt's lymphoma. The 20 NPC patients who were positive by skin test to HKLY-28 showed higher Ab titers to EBV nuclear antigen ($p < 0.001$) and lower ab titers to EBV early antigen ($P < 0.001$) than the 40 patients who were skin test-negative to HKLY-28. There were no significant differences in ab titers to EBV viral capsid antigen or in ab-dependent lymphocyte cytotoxicity. Among the BL patients there were no significant differences among those who showed negative or positive skin test responses to Raji cell line HMP. (13 refs)

- 79-5168 Inhibition by Phosphonoacetate of the In Vitro Outgrowth of Epstein-Barr Virus

Genome-containing Cell Lines from the Blood of Infectious Mononucleosis Patients. (Eng) Rickinson, A. B. (Dept. Pathology, Univ. Bristol Medical Sch., Bristol, England); Finerty, S.; Epstein, M. A. *IARC Sci Publ* 24(II): 721-728; 1978.

Experiments were undertaken to determine the extent to which Epstein-Barr virus (EBV) genome-containing cell lines in cultures of WBC from infectious mononucleosis (IM) patients arise through the direct in vitro outgrowth of cells transformed in vivo by the virus or, alternatively, through the transforming action of virus particles released into the culture medium by cells nonproductively infected in vivo. IM leukocytes were cultured under conditions specifically inhibitory to full virus replication. Phosphonoacetate (PA), added to the culture medium at 50 $\mu\text{g}/\text{ml}$, reduced EBV replication in producer cell lines to 1% of the control values, but it did not significantly affect the colony-forming ability of EBV-transformed cell lines or the efficiency of transformation of lymphocytes infected in vitro. When mononuclear cell preparations from IM blood were depleted of T cells and then cultured in the presence of 50 $\mu\text{g}/\text{ml}$ PA, the appearance of cell lines was almost totally inhibited; the occasional EBV genome-containing cell lines that appeared in PA-treated cultures after a long delay were composed of cells indistinguishable in terms of growth rate and morphology from cells arising in corresponding control cultures. In further experiments in which IM cells were cocultivated with fetal cells of opposite sex, the few cell lines that arose in PA-treated cultures were of mixed or of fetal origin, suggesting that they had arisen via the much reduced two-step mechanism and not through the direct outgrowth of IM cells already transformed by the virus in vivo. These results suggest that EBV nuclear antigen expression in circulating IM cells probably denotes the early stages of an infectious cycle rather than cellular transformation. (18 refs)

- 79-5169 Replication of Epstein-Barr Virus DNA in Epithelial Cells In Vivo. (Eng) Lemon, S. M. (Div. Infectious Disease, Dept. Medicine, Univ. North Carolina, Chapel Hill, NC); Hutt, L. M.; Shaw, J. E.; Li, J. L.; Pagano, J. S. *IARC Sci Publ* 24(II): 739-744; 1978.

Epstein-Barr virus (EBV)-specific complementary RNA (cRNA) was hybridized in situ to oropharyngeal epithelial cells taken from patients with infectious mononucleosis. Cells from patients shedding virus in the throat hybridized significant quantities of cRNA, whereas cells from EBV-negative sources did not. The degree of hybridization indicated a large EBV genome number per infected epithelial cell and suggested that these cells were the source of virus found in the throat. This finding may explain the presence of the EBV genome in the malignant epithelial cells of nasopharyngeal carcinoma patients. (12 refs)

79-5170 Cellular Immunity in Infectious Mononucleosis: I. Spontaneous and Phytohaemagglutinin-induced Blast Transformation in Infectious Mononucleosis, with Special Reference to Depressed Cellular Reactivity and Stimulation-blocking Serum Factors. (Eng) Nikoskelainen, (Dept. Medicine, Univ. Turku, Turku, Finland); Stevens, D. A.; Neel, E. U.; Isenberg, R. A.; Miller, R. G.; Halpern, J. W.; Gelpi, A. P. *IARC Sci Publ* 24(II): 699-709; 1978.

Lymphocytes of patients with infectious mononucleosis (IM), Epstein-Barr virus (EBV) seropositive subjects, patients with viral infections other than EBV, and EBV seronegative subjects were tested for phytohemagglutinin (PHA)-induced and spontaneous transformation in vitro. Lymphocytes of EBV seropositive healthy subjects, tested in autologous serum, had higher spontaneous transformation than those of EBV sero-negative subjects. IM patients, in the acute phase of illness, had depressed spontaneous lymphocyte transformation, independent of serum factors. Serum factors were present in acute IM that depressed spontaneous transformation further, and to a lesser extent depressed reactivity to PHA. By the time the IM patients had recovered (>9 weeks after onset of illness), the observed defects had disappeared. (15 refs)

79-5171 Detection of Epstein-Barr Virus-coded Antigens in Lymphocytes Isolated From Defined Patient Samples. (Eng) Veltri, R. W. (Dept. Surgery Microbiology, West Virginia Univ. Medical Center, Morgantown, WV); McClung, J. E.; Sprinkle, P. M. *IARC Sci Publ* 24(II): 729-732; 1978.

A preliminary report on the use of specific rabbit antisera raised to the Epstein-Barr virus (EBV) nuclear antigen (EBNA) and early antigen (EA) for detection of these antigens in vivo is presented. Human lymphocytes were isolated on isokinetic gradients; and the C3 receptor-bearing B-lymphocyte subpopulation was isolated, providing an enriched source of EBV-infected lymphocytes. Such technology was employed to establish the status of the EBV host-cell complex in recurrent exudative tonsillitis (RET), infectious mononucleosis (IM), and Hodgkin's and non-Hodgkin's lymphoma patients. Only EBNA was detected in the lymphocytes from the tonsils of RET patients and the peripheral blood of IM patients. However, the spleen and lymph nodes of lymphoma patients had lymphocytes synthesizing EBNA and EA. (12 refs)

79-5172 Twenty-One Years of Follow-up Studies of Familial Epidermodysplasia Verruciformis. (Eng) Jablonska, S. (Dept. Dermatology, Warsaw Sch. Medicine, Koszykowa 82a, 02-008 Warsaw, Poland); Orth, G.; Jarzabek-Chorzelska, M.; Glinski, W.; Obalek, S.; Rzeska, G.; Croissant, O.; Favre, M. *Dermatologica* 158(5): 309-327; 1979.

A 21-yr follow-up study of a family with epidermodysplasia verruciformis (EV) showed that members of one family can be infected with different human papillomaviruses (HPV's), either HPV-3 or HPV-4, or, sometimes, with both. Three generations of the family were affected. The clinical picture was that of disseminated flat warts in cases induced by HPV-3, whereas in those caused by HPV-4 there were flat red or red-brownish plaques and unpigmented pityriasis lesions. Malignancies developed only in family members infected with HPV-4, whereas the cases due to HPV-3 ran a more benign and slowly progressive or stationary course. There were also abortive and regressive cases, and the three children in whom the wartlike lesions did not recur after removal had an unimpaired cell-mediated immunity (CMI). In all cases of EV, irrespective of the inducing virus, CMI was low, a factor that seems to be important in the pathogenesis of the disease. Humoral antibodies directed specifically against HPV-3 were present in most of the cases, mainly in those infected with HPV-3. (37 refs)

79-5173 Role of Interferon in the Pathogenesis of Herpes Simplex Virus Disease in Mice. (Eng) Gresser, I. (Institut de Recherches Scientifiques sur le Cancer, Villejuif, France); Tovey, M. G.; Maury, C.; Bandu, M. T. *IARC Sci Publ* 24(II): 1049-1054; 1978.

The role of interferon in the pathogenesis of herpes simplex virus (HSV) disease was studied in pathogen-free Swiss and C3H mice. Iv administration of a sheep antimouse interferon globulin resulted in the early appearance of disease and death, and it increased the overall mortality due to HSV type 1 injected ip or sc. The enhancing effect was most striking when HSV was inoculated sc. Twenty-five mice that had survived HSV inoculation were injected iv with antiinterferon globulin 18 days after virus inoculation. In no instance did this treatment induce signs of HSV disease. These results demonstrate the importance of the early interferon response in the pathogenesis of HSV disease in mice. (7 refs)

79-5174 Replication of Herpes Simplex Virus in Human B Lymphocytes Stimulated by Epstein-Barr Virus. (Eng) Kirchner, H. (Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany); Schroder, C. H. *Intervirology* 11(1): 61-65; 1979.

The replication of herpes simplex virus (HSV) in human B lymphocytes stimulated by Epstein-Barr virus (EBV) is reported. Human WBC were obtained from unselected adult blood (AB) and cord blood (CB) samples and processed by a Ficoll-Hypaque technique. T and B cells were separated with the use of neuraminidase-treated sheep

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RBC. Two populations were obtained: population B, containing <2% of T cells, and population T, containing <2% B cells. The B and T cells were stimulated with phytohemagglutinin (PHA), pokeweed mitogen (PWM), or two strains of EBV, B95-8 and P3HT-1. B95-8 induced high levels of ³H-thymidine incorporation in CB and AB cultures of B cells. It was unreactive in the T cells. P3HR-1 was unable to induce DNA synthesis in either B or T lymphocytes. P3HR-1 suppressed DNA synthesis in B lymphocytes stimulated by B95-7. PWM or PHA did not stimulate purified B lymphocytes. When AB or CB B cells were preincubated for various periods of time in the presence of B95-8 and then infected with HSV, marked replication of HSV could be demonstrated. There was no HSV replication in B cells pretreated with P3HR-1 or in T cells pretreated by either EBV strain. However, after T cells were prestimulated with PWM, they were able to replicate HSV. Thus, both T and B cells can replicate HSV provided they are preactivated with the appropriate mitogen. Enriched monocyte populations (60%-70% monocytes, obtained after 2 cycles of plastic adherence) were unable to replicate HSV regardless of which mitogen was used. (16 refs)

79-5175 Virological and Serological Studies in Pregnancy, in Women with Suspect Genital Herpes Simplex Virus or Perinatal Cytomegalovirus Infections, and in Women with Carcinoma of the Cervix. (Eng) Frenkel, L. D. (Medical Coll. Ohio at Toledo, Toledo, OH); Crawford, M. A.; Bellanti, J. A. *IARC Sci Publ* 24(11): 911-915; 1978.

To assess the concomitant virological and serological markers of genital herpes simplex virus (HSV) and perinatal cytomegalovirus (CMV) infection, 25 pregnant women, 52 women with a history of recurrent HSV infection, 22 women with suspected CMV infection, 11 women with carcinoma of the cervix in situ (CIS), and 47 matched controls were studied. Urine and cervical viral cultures from normal controls and women with CIS yielded no HSV or CMV. HSV was isolated from three pregnant women and CMV was isolated from two pregnant women. CMV was isolated from six nonpregnant women, and HSV was isolated from 16 nonpregnant women, 2 of whom were also intermittently positive for CMV. Geometric mean titers (GMT) to CMV and HSV were slightly elevated in the pregnant subjects, and the percentage of seronegative pregnant women was considerably smaller than that of controls. GMT to CMV were significantly higher in women with suspected CMV and to HSV-1 and HSV-2 in women who had a history of recurrent herpes genitalis. GMT to all three viruses were elevated in women with CIS ($p < 0.005$), and none of them were seronegative. (10 refs)

79-5176 Poly(adenosine Diphosphate Ribose) Synthesis During Herpes Simplex Virus Infection.

(Eng) Muller, W. E. (Institut für Physiologische Chemie, Abteilung Angewandte Molekularbiologie, Duesbergweg, D-6500 Mainz, W. Germany); Falke, D.; Zahn, R. K.; Arendes, J. *Intervirology* 11(3): 182-187; 1979.

The effect of poly(adenosine diphosphate ribose) [poly(ADP-Rib)] synthesis on the synthesis of DNA in herpes simplex virus (HSV)-infected baby hamster kidney (BHK-21) cells was determined. Cellular DNA synthesis was blocked immediately after infection. After almost complete inhibition of host cell DNA formation at 3.5 hr postinfection, extensive HSV DNA synthesis began. These dramatic alterations of the control mechanisms for the two DNA-synthesizing systems were not accompanied by a significant change in poly(ADP-Rib) polymerase activity. Thus, during the suppression of cellular DNA synthesis and the onset of viral DNA synthesis, chromatin-bound and extractable poly(ADP-Rib) polymerase activity remained unaltered. Poly(ADP-Rib) may represent a structural element in the organization of chromatin and it may have some biological function in chromosome condensation during mitosis. (30 refs)

79-5177 Isolation and Localization of Herpes Simplex Virus Type 1 mRNA. (Eng) Anderson, K. P. (Dept. Molecular Biology and Biochemistry, Univ. California at Irvine, Irvine, CA 92717); Stringer, J. R.; Holland, L. E.; Wagner, E. K. *J Virol* 30(3): 805-820; 1979.

Two independent methods were used to determine the size ranges of specific herpes simplex virus type 1 (HSV-1) messenger RNA (mRNA) species synthesized late after infection and to localize individual transcripts to specific regions of the viral genome. Restriction fragments of HSV-1 DNA bound to cellulose were used to isolate viral mRNA for size analysis on denaturing agarose gels. Total viral polysomal polyadenylated RNA was isolated from cells late after infection, when this RNA has sequences encoded by approx 45% of the HSV DNA. This RNA has a size range of from 1.5 to ≥ 8 kilobases (kb), with certain sizes, such as 1.7 to 1.9 kb, being favored. The restriction endonucleases *Hind*III and *Xba*I were used singly and together to generate various-sized fragments covering the entire HSV-1 genome. These fragments were bound to cellulose to allow isolation of HSV-1 mRNA annealing to different regions of the viral genome. Discrete sizes of viral mRNA were associated with certain regions of the genome, but the mRNA population hybridizing to even the smallest restriction fragments was complex. Hybridization of size-fractionated RNA to Southern blots of restriction fragments of HSV-1 DNA generated by the *Bgl*II as well as *Hind*III and *Xba*I endonucleases was used to confirm the preparative hybridization data and to provide some overlap data for positioning transcripts. The data of blot and preparative hybridization agreed very well, and they were combined to construct a preliminary transcription map of HSV-1. This map revealed at least two areas of the long unique region of the HSV-1

genome that annealed to a large number of HSV-1 transcripts. Furthermore, discrete-sized mRNA species >5 kb long were found only in the middle of the long unique region. (39 refs)

- 79-5178 Alterations in the Protein Synthetic Apparatus of Cells Infected with Herpes Simplex Virus. (Eng) Silverstein, S. (Dept. Microbiology, Coll. Physicians and Surgeons, Columbia Univ., 701 W. 168th St., New York, NY 10032); Engelhardt, D. L. *Virology* 95(2): 334-342; 1979.

The effect of herpes simplex virus (HSV) infection on the rate of protein synthesis, the distribution of ribosomes, and the time required to complete nascent peptides (transit time) was examined in actively growing or stationary phase Vero cells. The rate of protein synthesis per polysomal ribosome decreased continuously throughout the early portion of the infection cycle. This occurred despite an increase in the accumulation of ribosomes in polysomelike structures that accompanies the onset of synthesis of HSV-specified proteins. Transit-time measurements demonstrated that the rate of polypeptide elongation was not altered after infection. These data are discussed in light of a model that suggests that polysomelike structures are present but not functioning (or functioning very poorly) in HSV-infected cells. (24 refs)

- 79-5179 Location of Non-Temperature-sensitive Genes on the Genetic Map of Herpes Simplex Virus Type 1. (Eng) Brown, S. M. (Medical Res. Council Virology Unit, Inst. Virology, Glasgow, Scotland); Jamieson, A. T. *IARC Sci Publ* 24(1): 33-39; 1978.

By constructing three-factor crosses involving the genes coding for deoxypyrimidine kinase and for resistance to the drug phosphonoacetic acid, it was possible to extend the genetic analysis of herpes simplex virus type 1 such that the eight possible progeny genotypes that arise from these crosses could be identified and to precisely locate the gene for the plaque-morphology marker (*sym*), the gene for deoxypyrimidine kinase (*dPyK*), and the gene for resistance to phosphonoacetic acid (*PAAr*). (3 refs)

- 79-5180 Characterization of Pyrimidine Deoxyribonucleoside Kinase (Thymidine Kinase) and Thymidylate Kinase as a Multifunctional Enzyme in Cells Transformed by Herpes Simplex Virus Type 1 and in Cells Infected with Mutant Strains of Herpes Simplex Virus. (Eng) Chen, M. S. (Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT 06510); Summers, W. P.; Walker, J.; Summers, W. C.; Prusoff, W. H. *J Virol* 30(3): 942-945; 1979.

Thymidylate kinase activity was studied in cells infected with herpes simplex virus type 1 (HSV-1) with mutations in the pyrimidine deoxyribonucleoside kinase [thymidine kinase (TK)] gene as well as in cells stably transformed to the TK⁺ phenotype. TK was purified from two HSV-1-transformed TK-deficient mouse (LMTK⁻) cell lines and from LMTK⁻ cells infected with HSV-1 mutant viruses coding for variant TK enzymes. These preparations exhibited normal or variant virus-induced thymidylate kinase activities correlating with their relative TK activities. Neither virus-induced activity was detected in LMTK⁻ cells infected with an HSV-1 TK-deficient mutant. These results suggest that a single HSV-1 gene codes for a multifunctional enzyme with thymidylate kinase activity and TK activity. (14 refs)

- 79-5181 Sequential Changes in Cell-mediated Immune Responses to Herpes Simplex Virus Following Primary Herpetic Infection in Man. (Eng) Shillitoe, E. J. (Dept. Oral Medicine and Hosp. Dentistry, Univ. California, Sch. Dentistry, San Francisco, CA); Wilton, J. M.; Lehner, T. *IARC Sci Publ* 24(11): 753-758; 1978.

Sequential changes in cell-mediated immune responses to herpes simplex virus type 1 (HSV-1) were studied in 5 patients with primary herpetic stomatitis, 2 patients with primary herpetic infection of the hand, and 19 normal controls. HSV-1 antibodies, which were detectable in only 2/6 patients at presentation, were detected in the sera of all patients 14-21 days after the onset of symptoms. The lymphocyte stimulation index in response to HSV-1 was significantly greater in patients who had symptoms for up to 7 days than in seropositive controls ($P < 0.02$). The response declined but was still greater than that of seronegative controls after 21 days ($P < 0.01$). Responses to purified protein derivative of tuberculin (PPD) and phytohemagglutinin were similar in patients and controls at presentation and 14 days later. Mean migration indices of supernatants of HSV- and of PPD-stimulated lymphocytes were similar among seronegative and seropositive controls and patients. However, macrophage migration inhibition increased between the first and last test performed on each patient ($P < 0.02$). The data suggest that recovery from herpetic infection coincides with the appearance of antibody and of macrophage migration inhibition and not with lymphocyte sensitization. (7 refs)

- 79-5182 Immunological Nature of Genetic Resistance of Mice to Herpes Simplex Virus Type 1 Infection. (Eng) Lopez, C. (Sloan-Kettering Inst. Cancer Res., New York, NY). *IARC Sci Publ* 24(11): 775-781; 1978.

Adult C57Bl/6 and A/J mice were studied to determine whether genetic resistance to herpes simplex virus type 1

(HSV-1) is immunologically mediated. The importance of T cells and macrophages in genetic resistance to HSV-1 was demonstrated. Lethally irradiated A/J mice (highly susceptible) given bone marrow transplants from resistant (C57Bl/6 x A/J)F₁ mice were more resistant to HSV-1 challenge than were untreated A/J mice. The in vitro capacity of isolated macrophages to restrict HSV-1 replication did not reflect in vivo resistance. There was a striking similarity between the capacity of mice to resist HSV-1 infections and their ability to resist allogeneic marrow grafts. The only major difference was that allogeneic resistance was more radioresistant than was resistance to HSV-1. (21 refs)

79-5183 The Alterations of PK and LDH Activities in the Cells Infected with Herpes Virus; The Effects of Anti-PK IgG and Anti-Herpes Serum on These Alterations. (Eng) Moldoveanu, N. (Inst. Biological Sciences, Splaiul Independenței 296, Bucharest, 77748 Romania); Tanasescu, D.; Nachtigal, M. *Rev Roum Biochim* 15(4): 305-309; 1978.

Pyruvate kinase (PK), lactate dehydrogenase (LDH), and protein levels were determined in cultures of HEp-2 cells infected with herpes simplex virus type 1 VR (prepared on rabbit kidney cell cultures) in the presence or absence of rabbit antiherpes serum or anti-PK IgG (obtained from chickens inoculated with purified bovine muscle PK). The protein content of virus-infected HEp-2 cells was similar to that of control cells during the first 12 hr, but it was significantly lower at 48 hr after inoculation. LDH and PK activities increased at 24 hr, but they showed significant decreases at 48 hr postinfection. The antiherpes serum and anti-PK IgG exhibited a protective effect against the virus-induced inhibition of protein and enzymes. (17 refs)

79-5184 Apparent Absence of Virus-specific Transplantation Rejection Antigen in Herpes Simplex Virus-transformed Hamster Cells. (Eng) Lausch, R. N. (Dept. Microbiology and Immunology, Coll. Medicine, Mobile, AL); Hay, K. A. *IARC Sci Publ* 24(II): 905-910; 1978.

The 14-012-8-1, T-10 cell line was used to determine whether cells transformed by herpes simplex virus type 1 (HSV-1) express transplantation rejection antigen and whether HSV-1 immunization influences the incidence of tumor metastases. Hamsters sensitized to the tumor cells by intradermal inoculations of 10⁵ cells, followed 10-15 days later, by excision of the tumor were resistant to low challenge doses of a subsequent isograft, as evidenced by reduced tumor incidence and increased latent period. Thus, the cells did express transplantation rejection antigen. However, immunization of hamsters with three inoculations of HSV-1 provided no significant protection against

challenge with low doses of 14-012-8-1, T-10 cells. Therefore, the transplantation antigen detected in the concomitant immunity experiments was not virus associated. Immunization with HSV-1 or HSV-2 did not appear to enhance or inhibit the incidence of tumor metastases in comparison with normal or cytomegalovirus-sensitized controls. (8 refs)

79-5185 Reduction of ⁵¹Cr-Permeability of Tissue Culture Cells by Infection with Herpes Simplex Virus Type 1. (Eng) Schlehofer, J. R. (Institut für Klinische und Experimentelle Virologie der WE04, Freie Universität Berlin, Hindenburgdamm 27, D-1000 Berlin 45, W. Germany); Habermehl, K. O.; Diefenthal, W.; Hampl, H. *Intervirology* 11(3): 158-166; 1979.

The protection of herpes simplex virus type 1 (HSV-1)-infected cells from immunological injury and from several cytotoxic agents was demonstrated. The infection of HEp-2, Chang liver, FL, baby hamster kidney (BHK-21), rabbit kidney, HeLa, and KB cells with HSV led to a significant reduction of ⁵¹Cr release (CR). This effect began 6-8 hr postinfection. In chick embryo fibroblasts (CEF), however, HSV infection enhanced CR. The HSV-induced reduction of CR indicated that the permeability of the cellular membrane was altered. This assumption was confirmed by the finding of reduced incorporation of ⁵¹Cr into infected cells. The effect began 8 hr postinfection and correlated with the onset of the reduction in CR and with the logarithmic increase in HSV replication. CR was not due to a loss of ⁵¹Cr during HSV penetration or other events early in infection. With the exception of CEF, HSV increased the stability of the cells toward Triton X-100. In addition, HSV-infected HEp-2 cells were resistant to toxic guinea pig serum and to HSV-specific complement-mediated immune cytolysis. The HSV-induced stability of cellular membranes may play a part in the maintenance of latent infection. (13 refs)

79-5186 Herpes Simplex Virus Latency in Patients With Multiple Sclerosis, Lymphoma and Normal Humans. (Eng) Warren, K. G. (Multiple Sclerosis Res. Center of the Wistar Inst., Univ. Pennsylvania, Philadelphia, PA); Devlin, M.; Gilden, D. H.; Wroblewska, Z.; Koprowski, H.; Brown, S. M.; Shubik-Sharpe, J. *IARC Sci Publ* 24(II): 765-768; 1978.

Herpes simplex virus (HSV) was isolated from the trigeminal ganglia (TG) of 12 cadavers (10 traumatic deaths, one lymphoma and one multiple sclerosis). The cadaver with multiple sclerosis showed large bilateral trigeminal nerve root entry zone areas of demyelination that may have been initiated by HSV. (5 refs)

- 79-5187 Herpes Virus Infection as a Cofactor in Carcinogenesis. Supernatants of Herpes Virus Type 1- and Type 2-infected Cell Cultures Contain a Cell Growth-stimulating Factor. (Eng) Reiss-Gutfreund, R. J. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria); Dostal, V.; Wenzel, J. *Oncology* 36(2): 55-62; 1979.

Following lytic infection with herpes simplex virus (HSV) type 1 or 2, some cell cultures synthesize a mitogenic factor (DNASF) that is shed into the medium. Of six cell lines permissive to HSV infection tested, three (CV1, HF, MCA) produced DNASF. In addition, significantly higher (³H)-thymidine incorporation was obtained with indicator cells growing in supernatants of virus-infected cells (SupV+) than in the corresponding supernatants of sham-treated cells (SupV-). In some cases, the values obtained with SupV+ exceeded those obtained with cell controls, which demonstrates that DNASF is not simply a nutritional factor. The cell lines that did not produce DNASF were HeLa, Wistar, and, probably, REF; SupV+ frequently inhibited cell growth in these lines. DNASF was genetically nonspecific, and all indicator cells tested were stimulated by supernatants that contained the mitogen, including the nonpermissive DC-3F cells. The quantity of DNASF induced was directly proportional to the number of cells in the culture, and its production peaked when cell lysis was complete. It did not accumulate inside the cells. (23 refs)

- 79-5188 Physical Mapping of Herpes Simplex Virus-coded Functions and Polypeptides by Marker Rescue and Analysis of HSV-1/HSV-2 Intertypic Recombinants. (Eng) Wilkie, N. M. (Dept. Virology, Inst. Virology, Univ. Glasgow, Glasgow, Scotland); Stow, N. D.; Marsden, H. S.; Preston, V.; Cortini, R.; Timbury, M. C.; Subak-Sharpe, J. H. *IARC Sci Publ* 24(1): 11-31; 1978.

Several temperature-sensitive (*ts*) mutants and one pyrimidine deoxyribonucleoside kinase-deficient mutant of herpes simplex virus (HSV) were located on the physical map of the genome by marker rescue experiments and by analysis of the crossover points in intertypic recombinants between HSV types 1 and 2. The physical map was compared with the genetic map, and certain anomalies were identified. Analysis of infected-cell polypeptides specified by intertypic recombinants allowed tentative map coordinates to be assigned to the structural genes (or genes that cause posttranslational modification) for many of the polypeptides. Immediate-early, phosphorylated, glycosylated, and structural as well as nonstructural polypeptides were analyzed in this way. It was concluded that there is no restriction of any of these groups of polypeptides to either the long or the short regions of the genome. One of the recombinants, 2853, is at least partially "frozen" in one orientation of the long region. This orientation is also the one that exhibits a minimum number of crossovers in three other recombinants. (28 refs)

- 79-5189 The Use of Intertypic Recombinants for Analysis of Gene Organization in Herpes Simplex Virus. (Eng) Morse, L. S. (Marjorie B. Kovler Viral Oncology Lab., Univ. Chicago, Chicago, IL); Pereira, L.; Roizman, B.; Schaffer, P. A. *IARC Sci Publ* 24(1): 41-61; 1978.

Herpesvirus type 1 (HSV-1) x HSV type 2 (HSV-2) recombinant DNA's with heterogeneous L and S components or with heterogeneous inverted repeats were studied to map the location of templates specifying the polypeptides on the HSV genome. HSV-1 and HSV-2 genes appeared to be functionally equivalent and with few exceptions were arranged colinearly. Colinear DNA maps were established. At most, two arrangements of HSV DNA were capable of replication. α Polypeptides mapped at the termini of the L and S components. Although α infected-cell polypeptide (ICP) 27 mapped entirely within the reiterated region of the L component, the template for α ICP 4 appeared to lie only in part within the reiterated sequences of the S component. Cells infected with a recombinant containing both HSV-1 and HSV-2 sequences in the S component produced α ICP 4 of both HSV-1 and HSV-2. Templates specifying β and γ polypeptides mapped in the L component and appeared to be distributed randomly. The genes specifying thymidine kinase, resistance to phosphonoacetic acid, and syncytial plaque morphology mapped in the L component. The gene(s) specifying the inhibition of host protein synthesis mapped in the L component. (35 refs)

- 79-5190 Immunoelectrophoretic Identification and Purification of Herpes Simplex Virus Antigens Released from Infected Cells in Tissue Culture. (Eng) Norrild, B. (Dept. Pediatrics, Emory Univ. Sch. Medicine, 69 Butler St. SE, Atlanta, GA 30303); Vestergaard, B. F. *Intervirology* 11(2): 104-110; 1979.

Proteins released from herpes simplex virus type 1 (HSV-1)- and type 2 (HSV-2)-infected HEP-2 cells have been characterized by the crossed immunoelectrophoretic technique. Both HSV type-common and type-specific antigens were found in the tissue culture medium 24 hr after infection. Antigen Ag-6, an HSV-1-specific antigen, was found in high concentration in the medium as compared to other HSV antigens released from HSV-1-infected cells. The HSV-2-specific antigens, Ag-4 and Ag-1, were released in molecular modifications with altered electrophoretic mobility as compared to their cellular counterparts. Purification of HSV antigens was performed by ion-exchange chromatography, and an HSV type-common antigen, Ag-11, and an HSV-2-specific antigen, Ag-4A, were isolated. (13 refs)

- 79-5191 Presence of Antibody Against Herpes Simplex Virus-specified Thymidine Kinase and Deoxyribonuclease in Human Sera. (Eng) Cheng, Y. C. (Dept.

Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY); Hoffmann, P. J.; Kung, M. P. *IARC Sci Publ* 24(11): 899-904; 1978.

Human sera were tested for their ability to inhibit the activity of herpesvirus type 1 (HSV-1) specific thymidine kinase (TK) and DNase and HSV-2 specific TK and DNase. All subjects who had experienced periodic fever blisters had antibody (Ab) against at least one of the virus-specified enzymes. Of 30 normal subjects, 4 had no inhibitory activity against any of the enzymes, 13 had activity against TK but not DNase, 1 had activity against DNase, and 12 had Ab against TK and DNase. Of 34 subjects with untreated prostatic, lung, or gastrointestinal tumors, 6 had Ab against TK and 28 had Ab against TK and DNase. With the exception of one patient, the inhibition of viral TK and DNase was type-specific. Of 13 patients with untreated, chronic myelocytic leukemia or Hodgkin's disease, 8 had Ab against TK, 3 had Ab against TK and DNase, and 2 had no activity against either enzyme. There was no evidence of cross-immunogenicity between TK and DNase derived from the same virus-infected cells. (17 refs)

79-5192 Experimental Infection of Tupaia with Herpes Simplex Virus Types 1 and 2. (Eng) Munk, K. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Schwaier, A.; Darai, G. *IARC Sci Publ* 24(11): 789-793; 1978.

The susceptibility of *Tupaia belangeri* to infection by herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) was studied. HSV was highly pathogenic for juvenile (28- to 40-day old) tupaia, resulting in death after 2-14 days. Death occurred earlier after iv than after ip or sc inoculation of HSV. The liver tissue of the diseased animals showed histomorphological changes resembling those of acute herpetic hepatitis. The spleen showed hyperemia, atrophy and fibrosis of the red pulp, and distinct necrotic changes. In some animals, the brain tissue showed edema, hyperemia, and hemorrhaging in the meninges, infiltration of lymphocytes, isolated cysts, and encephalitis. Viremia was observed 24-48 hr before death. Iv inoculation of HSV-2 into adult tupaia resulted in increased serum titers of neutralizing antibody but no symptoms of acute infection. Infectious virus was isolated from the lumbosacral segment of the spinal cord and gasserian ganglia of animals that survived HSV infection. (14 refs)

79-5193 Detection of Herpes Simplex Virus Type 2 mRNA in Human Cervical Biopsies by In Situ Cytological Hybridization. (Eng) Jones, K. W. (Inst. Animal Genetics, Univ. Edinburgh, Edinburgh, Scotland); Fenoglio, C. M.; Shevchuk-Chaban, M.; Maitland, N. J.; McDougall, J. K. *IARC Sci Publ* 24(11): 917-925; 1978.

In situ cytological hybridization was used to detect herpes simplex virus type 2 (HSV-2) messenger RNA (mRNA) in human cervical biopsies. The primary advantages of this method are direct examination of individual cells in smears or sections and amplification of target sequences as mRNA, provided that any integrated viral DNA is transcribed. Once optimal conditions are established for any particular virus, the in situ method will provide an extremely valuable means of detecting viral nucleic acid sequences in tumors. Of 8 cervical biopsy specimens (carcinoma or dysplasia) 5 were positive for HSV-2. (15 refs)

79-5194 Immune Responses to Vaginal or Systemic Infection of Mice with Herpes Simplex Virus Type 2. (Eng) Morahan, P. S. (Dept. Microbiology, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA); Breinig, M. C.; McGeorge, M. B. *IARC Sci Publ* 24(11): 759-763; 1978.

Relationships among cell-mediated immune (CMI) responses, neutralizing antibody, and macrophages in host resistance to vaginal or systemic infection with herpes simplex virus type 2 (HSV-2) were defined in BALB/c mice. The importance of T lymphocytes in resistance to either systemic or vaginal infection was demonstrated by the increased susceptibility of mice depleted of T lymphocytes. A role for nonspecific resistance against systemic, but not vaginal, infection was demonstrated by the increased susceptibility of mice depleted of macrophages. The temporal relationships among the serum antibody, delayed-type hypersensitivity, and splenic proliferative CMI responses were defined in individual animals. Vaginal infection was associated exclusively with relatively transient CMI responses that appeared during the acute infection. After systemic infection, CMI responses appeared during the acute infection and persisted for approx 5 wk; a humoral response appeared in surviving animals and persisted for at least 4 mo. The results suggest that CMI is the predominant host response to vaginal HSV-2 infection and that both CMI and macrophage-mediated antiviral activity may be involved in recovery from primary systemic infection with HSV-2. (12 refs)

79-5195 Growth of Type 2 Herpes Simplex Virus in Newborn and Adult Mononuclear Leukocytes. (Eng) Trofatter, K. F. (Dept. Pathology, Duke Univ. Medical Center, Box 3712, Durham, NC 27710); Daniels, C. A.; Williams, R. J.; Gall, S. A. *Intervirology* 11(2): 117-123; 1979.

Growth of type 2 herpes simplex virus (HSV) in newborn and adult human mononuclear leukocytes (MNL) was compared. Phytohemagglutinin stimulation of cultures for 3 days yielded comparable peak titers in newborn [$10^{5.3}$ plaque-forming units (PFU)] and adult ($10^{5.1}$ PFU) MNL.

Unexpectedly, 3-day cultures of unstimulated newborn MNL also substantially replicated HSV ($10^{4.7}$ PFU), whereas similarly treated unstimulated adult cells did not. Growth of HSV in freshly isolated human MNL was investigated. MNL from 4 mothers and 6 nonpregnant adults showed no evidence of virus growth; however, leukocytes from 11 of 24 newborns (46%) supported replication. Newborn MNL manifested an increased ability to replicate HSV within 1 day of culture, whereas comparable growth in adult MNL was not achieved until the 4th day of culture. The significance of the above observations as it relates to visceral dissemination of HSV in the neonate is discussed. (26 refs)

- 79-5196 Stimulation of Chemical Carcinogenesis in Mice Chronically Infected with Herpes Simplex Virus Type 2. (Rus) Kitsak, V. Ia. (Central Inst. Advanced Training Physicians, Moscow, USSR); Moisiadi, S. A.; Bocharov, A. F. *Vopr Virusol* (3): 277-282; 1979.

The role of herpes simplex virus type 2 (HSV-2) in the etiology of chemically induced tumors was evaluated. Albino mice were inoculated sc with 20-methylcholanthrene (20-MC: 0.1 mg) and/or HSV-2 (at 70 times the LD_{50}). Tumors induced by 20-MC (alone or with HSV-2) were first recorded 74-81 days later; tumor incidence was max on days 94-122. 20-MC alone induced tumors in 29.5% of mice weighing 10-12 g (younger mice) and in 41.8% of mice weighing 25-30 g (older mice). HSV-2 alone had no carcinogenic activity. The combined administration of 20-MC and HSV-2 significantly increased the incidence of tumors (68.0% in younger mice and 66.6% in older mice). (26 refs)

- 79-5197 Classification of Human Adenoviruses by SDS-Polyacrylamide Gel Electrophoresis of Structural Polypeptides. (Eng) Wadell, G. (Dept. Virology, Karolinska Institutet, S-105 21 Stockholm, Sweden). *Intervirology* 11(1): 47-57; 1979.

Analysis of the polypeptide patterns of 15 human adenovirus serotypes by sodium dodecyl sulfate-polyacrylamide gel electrophoresis showed that capsid polypeptides 11, 111, 111a, and IV display a pattern of apparent mol wts that is characteristic for each adenovirus serotype analyzed. The results also suggested the feasibility of obtaining a subgroup classification based on the apparent mol wts of internal polypeptides V, VI, and VII and, to some extent, on the size of the hexon (polypeptide II) and the vertex capsomer (polypeptide III). (32 refs)

- 79-5198 High Molecular Weight Virus DNA in KB Cells Infected with *ts* Mutants of Adenovirus Type 2 under Permissive and Non-Permissive Conditions. (Eng) Schick, J. (Inst. Genetics, Univ. Cologne, Cologne, W. Germany); Doerfler, W. *J Gen Virol* 43(part 1): 217-222; 1979.

Temperature-sensitive mutants (*ts206* and *ts214*) of adenovirus type 2 (Ad2) which were deficient in virus DNA synthesis at the nonpermissive temperature were used to determine whether virus DNA replication is required for the occurrence of high mol wt Ad2 DNA (> 100S, 50-90S) in human KB cells productively infected with Ad2. Ad2-specified DNA sequences could be detected in all four size classes of newly synthesized DNA in cells infected with wild-type Ad2. After infection with *ts206* or *ts214*, the amount of 34S wild DNA synthesized at the nonpermissive temperature was reduced 15- to 34-fold compared to synthesis at the permissive temperature. The quantities of viral DNA sequences in the < 20S size class were reduced 16- to 22-fold at the nonpermissive temperature. The amount of viral DNA sequences in the high mol wt size classes were reduced only 3- to 4-fold at the nonpermissive temperature. These reductions tended to be even lower in the > 100S size class. Thus, unabated viral DNA replication is not a prerequisite for the integration event. Under conditions which allow the synthesis of a large number of virus genome copies, linkage of viral DNA sequences to cellular DNA might occur more frequently because of the larger pool of free viral DNA. (11 refs)

- 79-5199 Mosaic Adenovirus-SV40 RNA Specified by the Non-defective Hybrid Virus Ad2+ND₄. (Eng) Westphal, H. (Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014); Lai, S. P.; Lawrence, C.; Hunter, T.; Walter, G. *J Mol Biol* 130(3): 337-351; 1979.

The structures of the simian virus 40 (SV40)-specific RNA's isolated from the cytoplasm of HeLa cells infected with the nondefective adenovirus 2-SV40 hybrid Ad2+ND₄ were determined by annealing the isolated RNA to Ad2, Ad2+ND₄, or SV40 DNA and examining the hybrids under an electron microscope. (The largest insert of SV40 DNA, comprising SV40 map positions 59 to 11, is found in Ad2+ND₄ DNA.) An attempt was made to establish in what way the structures of the SV40-specific RNA's allow the expression of proteins related to tumor antigen but not normally specified by SV40. A considerable proportion of the RNA was mosaic, consisting of Ad2 sequences at its 5' end and of SV40 RNA in the remainder of the molecule. The Ad2 sequences represented transcripts of separate segments of DNA. They started with the familiar tripartite leader of late Ad2 messenger RNA (mRNA), followed by various combinations of three separate sequences that are located between Ad2 map positions 75 and 79, preceding the SV40 insertion in Ad2+ND₄. The SV40

sequences within Ad2 + ND₄ RNA were often transcribed from noncontiguous segments as well. Some of these segments corresponded to those reported for RNA expressed by SV40 itself in early infection, others were quite different. The specific SV40 sequence arrangements in the mosaic RNA's allowed them to be correlated with individual translation products found in the infected cell. The intervening sequence common to SV40 and Ad2 + ND₄ was bounded by SV40 map positions 60 and 54. A deletion comprising this sequence was found in 80% of the Ad2 + ND₄ stocks. Sequences between 54 and 59 SV40 map units may be detrimental to the growth of Ad2 in human cells; ie, the presence of these sequences might interfere with the efficient processing of Ad2 transcripts into fiber mRNA, a gene that is downstream of the SV40 insertion. (33 refs)

- 79-5200 Human Brain Tumour Cell Strains with Deficient Host-Cell Reactivation of N-Methyl-N'-nitro-N-nitrosoguanidine-damaged Adenovirus 5.** (Eng) Day, R. S. (Nucleic Acids Section, Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Ziolkowski, C. H. *Nature* 279(5716): 797-799; 1979.

To evaluate the hypothesis that human tumorigenesis is often associated with repair-deficient cells, the survival of adenovirus 5 (Ad5) treated in vitro with the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was studied in various types of human host cells. Ad5 was suspended in a soln of 0.5-2.0 mg/ml MNNG for 30 min at 37 C, viral inactivation was terminated with N-acetyl-L-cysteine, and plaque assays were performed. Cells from 4/13 brain tumor strains (A172, A382, U-87MG, and U-105MG, from a glioblastoma and 3 astrocytomas, respectively) resulted in less survival of MNNG-damaged viruses than did the cells of the remaining brain tumor strains and the cells of 20 strains prepared from other human tumors or unaffected human organs. Among host cell strains that showed normal reactivation of MNNG-damaged Ad5 were skin fibroblasts from patients with ataxia telangiectasia (3) and xeroderma pigmentosum (1); cells from patients with brain (9), kidney (3), and liver (1) tumors and with leukemia (2); and cells from three brain tumor-prone families. Strains A172, U-87MG, and U-105MG had normal host-cell reactivation of UV-irradiated viruses. The results were interpreted to mean that the A172, A382, U-87MG, and U-105MG cell strains are defective in their ability to repair MNNG-damaged Ad5. It is suggested that the repairable lesion may be a DNA-N-nitrocyanamide reaction product. (21 refs)

- 79-5201 Adenovirus Type 12 VA RNA. I. Synthesis in Productive Infection and Gene Mapping.** (Eng) Fohring, B. (Fachbereich Biologie, Universitat

Kaiserslautern, W. Germany); Geis, A.; Koomey, M.; Raska, K. *Virology* 95(2): 295-302; 1979.

Virus-associated (VA) RNA synthesized late in adenovirus type 12 (Ad12)-infected cells was analyzed by two-dimensional polyacrylamide gel electrophoresis and by a sequence of three different gel electrophoresis separations. Each of these procedures resolves two distinct VA RNA species in Ad2-infected cells; however, no minor species was detected in either the nuclei or cytoplasm of Ad12-infected KB cells. VA RNA synthesized in vitro in isolated nuclei of KB cells 18 hr after Ad12 infection also showed only one distinct species upon electrophoretic analysis. VA RNA synthesis in isolated nuclei was resistant to α -amanitin at a concentration of 1 μ g/ml, but it was inhibited by a high concentration of α -amanitin (100 μ g/ml), which indicates that Ad12 VA RNA is synthesized by RNA polymerase III. The gene for VA RNA was mapped on the Ad12 genome by blot hybridization experiments. It is located around map unit 0.30, as determined by hybridization to fragments G and H of the *Bam* HI digest of Ad12 DNA. T₁ ribonuclease oligonucleotide fingerprint analysis of RNA selected by hybridization to fragments G and H failed to provide evidence for two species of VA RNA of distinctly different structure in this adenovirus serotype. (29 refs)

- 79-5202 Comparison of Late mRNA Splicing among Class B and Class C Adenoviruses.** (Eng) Kilpatrick, B. A. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724); Gelinas, R. E.; Broker, T. R.; Chow, L. T. *J Virol* 30(3): 899-912; 1979.

Experiments in which leader sequences for the *r*-strand late messenger RNA's (mRNA's) of class B serotype adenoviruses were mapped are described, along with experiments in which sequence relationships among the late RNA leaders of class B and class C serotypes were compared. Adenovirus class B (Ad3 and Ad7) and class C (Ad1, Ad5, and Ad6) late *r*-strand mRNA's were found to have segmented 5' leaders. These leaders were very similar among serotypes within a class, but they differed in sequence from the leaders on late mRNA's of a different class. However, the leader components of class B viruses mapped at essentially the same map coordinates as those of class C viruses. The 5' coordinates of the main bodies of class B messages to which the tripartite leaders are attached as well as the map positions of several of their early mRNA's were very similar to those of Ad2 transcripts. Infrequent examples of late *r*-strand polysomal RNA's of Ad3 and Ad7 had, in addition to the three common leader segments, a fourth leader segment derived from RNA encoded at various sites between the second and third leaders. The extra components formed several distinct groups. These molecules are presumably intermediates in the splicing processes that generate mature messages. (41 refs)

- 79-5203 Polyoma DNA Synthesis in Isolated Nuclei: Evidence for Defective Replication Forks. (Eng) Bjursell, G. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Munck, V.; Therkelsen, A. J. *J Virol* 30(3): 929-932; 1979.

A study was conducted to analyze how faithfully replication of polyoma DNA in a well-characterized nuclear system follows the bidirectional pathway. Nuclei isolated from polyoma virus-infected mouse 3T6 cells were incubated under conditions suitable for polyoma DNA synthesis. Electron microscopy and standard regression statistics showed that replication was mainly unidirectional in a large number of molecules, which indicates that inactive replication forks were present. The replication forks were inactivated randomly, and the defect seemed to be present from the beginning of the in vitro incubation. However, additional inactivation of forks might occur throughout the incubation. Each DNA segment from the origin to the terminus consisted of forks moving at different rates, and many forks passed through the termination site. Since a significant fraction of the replicative intermediates contained one impaired fork, it is suggested that two active forks are needed for proper termination. (22 refs)

- 79-5204 Structure of Polyoma Virus mRNAs Synthesized in Productively Infected Mouse Cells. (Eng) Kamen, R. (Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, P.O. Box 123, London WC2A 3PX, England); Favaloro, J.; Parker, J.; Treisman, R.; Flavell, A. J.; Cowie, A.; Legon, S. *Differentiation* 13(1): 45-46; 1979.

Recent studies of the topography of polyoma virus transcripts illustrate three principles. (1) Viral messenger RNA's (mRNA's) synthesized early in productive infection are a family of RNA's related by differential internal splicing, which allows a single continuous DNA sequence in the viral genome to encode a minimum of three different polypeptide chains; (2) viral mRNA's synthesized late in productive infection are a further family of three mRNA's related by "leader sequence transfer"; and (3) the structure of the "leader" sequences attached to the three late mRNA's demonstrates the principle of 5'-terminal heterogeneity, and it shows that posttranscriptional processing can generate tandemly repeated RNA sequences that constitute a sequence amplification with respect to the viral DNA sequence. (26 refs)

- 79-5205 Factors Affecting the Formation of Polyoma Pseudovirions. (Eng) Cashdollar, L. W. (West Virginia Univ., Morgantown, WV). *Diss Abstr Int [B]* 39(11): 5236; 1979 (no refs)

- 79-5206 Influence of Inactivated Sendai Virus on Early Events in Polyomavirus Infection of Permissive and Nonpermissive Host Cells. (Eng) Artamonova, V. (Lab. Virus Etiology Tumors, Gamaleya Inst. Epidemiology and Microbiology, Moscow, USSR); Shevliaghin, V. *Intervirology* 11(6): 351-358; 1979.

A quantitative radiochemical investigation was made of the effect of β -propiolactone-inactivated Sendai virus (SV) on early events in polyomavirus infection of permissive (mouse embryo fibroblasts) and nonpermissive (chicken and human embryo fibroblasts) cells. These experiments showed that (1) SV did not increase polyomavirus adsorption on permissive or nonpermissive cells; (2) SV induced polyomavirus elution from permissive and nonpermissive cells during the first 40 min and 6 hr postinfection, respectively; and (3) SV promoted the penetration of polyomavirus into lysosomes only in nonpermissive cells. The max amounts of radioactively labeled virion DNA and viral coat proteins were found in lysosomes at 2-3 hr postinfection. (16 refs)

- 79-5207 Cellular and C-Type Viral Factors in Infections by Polyoma Virus *hr-t* Mutants. (Eng) Goldman, E. (Dept. Medical Microbiology, Univ. California at Irvine, California Coll. Medicine, Irvine, CA 92717); Hattori, J.; Benjamin, T. *Virology* 95(2): 373-384; 1979.

The effects of endogenous cellular and C-type RNA viral factors on the growth and transforming properties of polyoma virus *hr-t* mutants were examined. Moloney murine leukemia virus (MuLV) confers a permissive state on 3T3 cells, enhancing the growth of the *hr-t* mutant NG-18. However, MuLV infection of normal rat kidney (NRK) cells does not enable NG-18 to transform these cells. Fv-1 restriction, pretreatment of cells with mitomycin C, or serum starvation after MuLV infection all prevent MuLV from inducing the permissive state in 3T3 cells. Primary mouse embryo cells, which are constitutively permissive for *hr-t* mutant growth, and primary rat or hamster embryo cells are not able to be transformed by *hr-t* mutants. These mutants are unable to induce either lectin agglutinability or transformation in a variety of mouse cells that are permissive for *hr-t* mutant growth. It thus appears that endogenous cellular factors or exogenous MuLV infections in mouse cells induce a permissive state, thereby enhancing the growth of *hr-t* mutants that are presumed to have lost the ability to induce that state. These factors act only to bypass the need for the *hr-t* function in polyoma virus growth, and they do not restore *hr-t* viral gene activity in inducing transformation and related cellular properties. The results are discussed in terms of a model proposed earlier for pleiotropic regulation of cellular factors by the *hr-t* viral gene. (31 refs)

- 79-5208 Infectivity in Mouse Fibroblasts of Polyoma DNA Integrated into Plasmid pBR322 or Lambdaoid Phage DNA. (Eng) Fried, M. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2, England); Klein, B.; Murray, K.; Greenaway, P.; Tooze, J.; Boll, W.; Weissmann, C. *Nature* 279(5716): 811-816; 1979.

The construction of various plasmid pBR322 and phage λ derivatives containing polyoma (Py) DNA and the infectivity of these derivatives toward mouse fibroblast cells are reported. Hybrid plasmid molecules were made with DNA from a Py mutant that lacked an *Hha* restriction site by digestion with restriction enzymes *Eco*RI or *Bam*HI and ligation to cleaved pBR322. *Escherichia coli* HB101 was transformed with the recombinant DNA, and colonies containing Py DNA were identified by hybridization to 32 P-labeled Py RNA. Py DNA was also inserted into DNA from several bacteriophage λ derivatives. Of the Py-pBR322 hybrids joined through the *Bam*HI site, those containing one unit length of Py virus DNA gave <1 plaque-forming unit/ μ g hybrid DNA, but cleavage of the hybrids with *Bam*HI resulted in a specific infectivity similar to that of the viral DNA cleaved with *Bam*HI. Similar results were obtained with 5/6 hybrids containing monomers of Py virus DNA joined to pBR322 through the *Eco*RI cleavage site. Hybrids containing 2 or 1.9 tandem head-to-tail genomes of Py virus DNA were infectious (10% and 1% as infectious as intact form I viral DNA, respectively). Py virus was isolated from several cell cultures that had been infected with the restricted plasmid containing monomeric Py DNA or with the unrestricted plasmid containing dimeric Py DNA. The results for the infectivity of the Py- λ hybrids before and after restriction were essentially the same as those for the monomer Py-pBR322 hybrids. The fact that cloned Py DNA, when excised at the site of joining, has an infectivity very similar to that of form III DNA derived from Py virions is evidence for the remarkable fidelity of the cloning procedure and the stability of a eukaryotic sequence replicated in a prokaryotic host. (26 refs)

- 79-5209 Effect of Mitomycin C and 60 Co γ -Irradiation on the Replication of SV40 in Cell Lines of Varying Permissivity for SV40 Replication. (Eng) Rakusanova, T. (Dept. Pediatrics, St. Elizabeth's Hosp., Boston, MA 02135); Smales, W. P.; Kaplan, J. C.; Black, P. H. *J Gen Virol* 43(part 1): 235-239; 1979.

The effects of mitomycin C and 60 Co γ -irradiation, which induce production of SV40 from SV40-transformed hamster cells, on the replication of superinfecting SV40 or the virus DNA in cells varying in permissivity for SV40 replication have been examined. These agents enhance replication of SV40 in an uninducible line of SV40-transformed hamster kidney cells and in nonpermissive secondary hamster kidney cells. The same treatments do not affect SV40 replication in semipermissive hamster

(BHK21) and human (HEL, HEK) cells and inhibit SV40 replication in permissive monkey (TC-7) cells. It is concluded that forms of induction treatment, such as mitomycin C or 60 Co γ -irradiation, modify the expression of host cell factors which determine the level of permissivity for SV40 infection. (9 refs)

- 79-5210 Effect of Azacytidine in SV40-Infected BSC-1 Cells. (Eng) Reuveni, Y. (Dept. Microbiology, Vincent T. Lombardi Cancer Center, Georgetown Univ., Sch. Medicine, Washington, DC 20007); Rosenthal, L. J. *Intervirology* 11(3): 191-195; 1979.

The effect of 5-azacytidine (5-AC, 25-300 μ g/ml) on simian virus 40 (SV40) messenger RNA transcription was studied following treatment of SV40-infected BSC-1 cells. The ribosomal 28S and 18S RNA's decreased with increasing 5-AC concentration, maximal inhibition occurring at 200-300 μ g/ml. After treatment with 200 μ g/ml 5-AC for 2 hr, virus-specific RNA in the 19S and 16S RNA region increased from 3.6% to 28%-36%. This was due to a 70%-75% reduction in ribosomal RNA's in the cytoplasm of the infected cells. (9 refs)

- 79-5211 Functional Characterization of the Early and Late mRNAs of Simian Virus 40. (Eng) Hunter, T. (Tumor Virology Lab., Salk Inst., P.O. Box 1809, San Diego, CA 92112). *Virology* 95(2): 511-522; 1979.

Early simian virus 40 (SV40) messenger RNA's (mRNA's) were characterized by size fractionation on acrylamide gels followed by in vitro translation and immunoprecipitation. The mRNA for the 17,000-dalton (17K) tumor (T) antigen migrated more slowly than that for the 100K T antigen, with the apparent size difference being 250 nucleotides. This finding is consistent with the mRNA for the 17K T antigen corresponding to an almost complete copy of the early region; the mRNA for the 100K T antigen probably lacks the sequences between 0.59 and 0.54 map units. The synthesis of any antigen intermediate in size between the 100K and 17K T antigens could not be detected by translation of SV40-specific RNA followed by immunoprecipitation. The synthesis of two proteins from intracellular SV40-specific mRNA's was demonstrated. They appeared to be identical to the VP2 and VP3 found in the virion on the basis of their mobilities in acrylamide gels and their tryptic peptide maps. Both VP2 and VP3 were labeled with formyl-[35 S]methionine when synthesized in the presence of [35 S]fMet-tRNA^{fMet}. When the partial proteolysis products of these N-terminally labeled proteins were analyzed, it was shown that VP2 and VP3 shared common C termini. Therefore, VP3 is initiated and made independently of VP2 and is not derived from VP2 by proteolytic processing. VP2 and VP3 are both made from mRNA's about 19S in

size. The mRNA for VP2 migrated marginally more slowly than the mRNA for VP3 in acrylamide gels. (38 refs)

- 79-5212 Nucleotide Sequence Analysis of Two Simian Virus 40 Mutants with Deletions in the Region Coding for the Carboxyl Terminus of the T Antigen. (Eng) Van Heuverswyn, H. (Lab. Molecular Biology, State Univ. Ghent, B-9000 Ghent, Belgium); Cole, C.; Berg, P.; Fiers, W. *J Virol* 30(3): 936-941; 1979.

The nucleotide sequence of two simian virus 40 early mutants, *d11263* and *d11265*, which lack a DNA segment around map positions 0.21 and 0.18, respectively, was analyzed. To characterize these deletions at the nucleotide level, each mutant DNA was digested separately with the restriction endonucleases *Hind*III + *I*II, *Hae*III, and *Alu*I. In-phase deletions of 33 nucleotide pairs for *d11263* and 39 nucleotide pairs for *d11265* were found. The 33-base pair deletion in *d11263* did not account for the apparent 6,000-dalton reduction in size observed for the large tumor (T) antigen induced by this mutant. In *d11265*, the normal termination signal as well as most of the proline-rich terminal tryptic peptide had been removed, and the carboxyl terminus of the mutant T antigen was a series of three cysteine residues. (21 refs)

- 79-5213 Nucleotide Sequence Analysis of Viable Deletion Mutants Lacking Segments of the Simian Virus 40 Genome Coding for Small t Antigen. (Eng) Thimmappaya, B. (Dept. Microbiology, Univ. Connecticut Health Center, Farmington, CT 06032); Shenk, T. *J Virol* 30(3): 668-673; 1979.

Direct DNA sequence analysis was used to map the deletions in nine viable simian virus 40 mutants. The mutant DNA's lack small segments of the early region of the viral chromosome (between 0.535 and 0.600 map units). The deletions are all located in the region that is removed from the large tumor (T)-antigen transcript by splicing. No one deletion removes this entire region, but no part of this segment is conserved in all of the mutants except for several nucleotides near the splice points of the transcript. Although the deletions do not alter the region coding for the large T polypeptide, they do delete portions of the segment coding for the C-terminal half of the small t polypeptide. (20 refs)

- 79-5214 Nucleotide Sequence Deletions Within the Coding Region for Small-t Antigen of Simian Virus 40. (Eng) Volckaert, G. (Lab. Molecular Biology, State Univ. Ghent, B-9000 Ghent, Belgium); Feunteun, J.; Crawford, L. V.; Berg, P.; Fiers, W. *J Virol* 30(3): 674-682; 1979.

Simian virus 40 early mutants with deletions mapping in the 0.53-0.60 region were sequenced by the Maxam and Gilbert approach. All these deletions affect the small tumor (t) gene. The size of the shortened small t-related polypeptides produced by several of the mutants was compared with the mol wt, as deduced from the nucleotide sequence. There was good agreement for the mutants *d890*, *d891*, and *d12102*. For *d12121* and *d12122*, the small t-related protein was considerably larger than expected. It is possible to explain this result on the basis of the nucleotide sequence: the normal splicing event of the small t messenger RNA (mRNA) still occurs, but as the deletion shifts the reading frame, translation of the small t-related polypeptide continues beyond the small t splice, but in a different reading frame than that for large T antigen. Mutants *d883*, *d884*, and *d12112* have lost one of the small t splicing boundaries, and no (or minute amounts of) small t-related protein was observed in mutant-infected cells. There may be a relationship between splicing and transport of polyadenylic acid-containing mRNA from the nucleus to the cytoplasm in vertebrate cells. (31 refs)

- 79-5215 Simian Virus 40 Mutants with Deletions at the 3' End of the Early Region Are Defective in Adenovirus Helper Function. (Eng) Cole, C. N. (Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Crawford, L. V.; Berg, P. *J Virol* 30(3): 683-691; 1979.

The ability of viable mutants of simian virus 40 (SV40) that contain deletions at various sites in the viral DNA to enhance adenovirus type 2 (Ad2) growth in CV-1 monkey cells was examined. Only mutants with deletions near the 3' end of the early region were deficient in providing this helper function. Mutants *D11265*, lacking 39 base pairs at map position 0.18, and *D11263*, lacking 33 base pairs at map position 0.20, were approx 4% and 30% as effective as wild-type SV40, respectively. The extent of enhancement of Ad2 yield depended on the multiplicity of infection by SV40, but not by Ad2 (at a multiplicity of infection of ≤ 50), as well as on the relative times of infection by Ad2 and SV40. Increasing the SV40 multiplicity of infection or infecting cells with SV40 wild type or mutants prior to Ad2 infection increased the Ad2 yield dramatically. The tumor (T) antigens of wild-type SV40, *D11263*, and *D11265* were examined. An attempt was made to correlate defects in helper function, alterations in the T-antigen structure, and the DNA sequence of the mutants as determined previously. (42 refs)

- 79-5216 T-Antigen Expression in Proliferating and Non-proliferating Simian Virus 40-transformed Mouse Cells. (Eng) Zouzas, D. (Dept. Pathology, New York Univ. Sch. Medicine, New York, NY 10016); Basilico, C. *J Virol* 30(3): 711-719; 1979.

Temperature-sensitive simian virus 40-transformed mouse 3T3 cells (ts SV3T3 cells) were used to study the expression of the viral genome under proliferating and non-proliferating conditions, in the presence and absence of inhibitors of macromolecular synthesis and of the tumor promoter phorbol myristate acetate. These cells express the transformed phenotype at 32 C and lose most or all of their transformed growth characteristics at 39 C. ts SV3T3 cells that were growth-arrested at 39 C by low serum concentration or saturation density accumulated in G1 and did not express tumor (T) antigen. When these cells were induced to proliferate at either 32 or 39 C, T-antigen synthesis preceded the entry of the cells into the S phase, and it was not coupled to DNA replication. G1-arrested ts SV3T3 cells were induced to synthesize T antigen by phorbol myristate acetate treatment (0.1 µg/ml, but antigen synthesis was not followed by cellular DNA synthesis. This suggested that T antigen may act as an inducer of cell proliferation, rather than as a direct initiator of DNA replication. Isoleucine deprivation arrested the growth of the ts SV3T3 cells, but these cells, as well as normal 3T3 cells, did not accumulate in G1 and they continued to express T antigen. The temperature-sensitive expression of the transformed phenotype in the ts SV3T3 cells does not appear to be due to a lack of transcription of specific regions of the integrated simian virus 40 genome at 39 C. (40 refs)

- 79-5217 Biology of Simian Virus 40 (SV40) Transplantation Antigen (TrAg). IV. Inhibition by Human Interferon of Expression of SV40 TrAg in SV40-infected Monkey Cells. (Eng) Tevethia, S. S. (Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Greenfield, R. S.; Rieder, V.; Tevethia, M. J. *Virology* 95(2): 587-592; 1979.

Treatment of African green monkey kidney cells with human interferon prior to simian virus 40 (SV40) infection inhibited the expression of SV40 transplantation antigen (TrAg) as well as tumor (T) antigen. The inhibition occurred in SV40-infected but not in SV40-transformed monkey cells. The synthesis of SV40 T antigen as detected in the indirect immunofluorescence test and of large and small T antigens as detected by immunoprecipitation with sera from tumor-bearing hamsters and electrophoresis in sodium dodecyl sulfate-gels was similarly affected in SV40-infected monkey cells. These results suggest that the induction of SV40-specific TrAg in the cytolytic cycle depends upon a viral, rather than a host, message. (26 refs)

- 79-5218 Biochemical and Immunochemical Characterization of Two Simian Virus 40 (SV40)-specific Glycoproteins in Nuclear and Surface Membranes of SV40-transformed Cells. (Eng) Schmidt-Ullrich, R. (Therapeutic Radiology Dept., Radiobiology Div., Tufts-New England Medical Center, 171 Harrison

Ave., Boston, MA 02111); Thompson, W. S.; Wallach, D. F. *Biochem Biophys Res Commun* 88(3): 887-894; 1979.

Biochemical and immunochemical techniques were used to characterize the membrane proteins of simian virus 40 (SV40)-transformed cells. The plasma membranes of several SV40-transformed cells contained virus-specific proteins with mol wts of approx 100,000 and 60,000 daltons and isoelectric points of approx 4.7 and 4.5, respectively. Triton X-100 extracts of purified nuclei from SV40-transformed hamster lymphocytes contained the same proteins but in different proportions, the high mol wt component being increased sixfold compared with the lower mol wt one. Both proteins could be labeled metabolically with [¹⁴C]glucosamine and their isoelectric points could be altered by neuraminidase treatment, which indicates that they are sialoglycoproteins. (21 refs)

- 79-5219 Phospholipids in Cell-substratum Adhesion Sites of Normal, Virus-transformed and Revertant Murine Fibroblasts. (Eng) Cathcart, M. K. (Case Western Reserve Univ., Cleveland, OH). *Diss Abstr Int [B]* 39(11): 5236-5237; 1979 (no refs)

- 79-5220 Differences in the Surface Components of Normal and SV-40 Transformed 3T3 Mouse Fibroblasts. (Eng) Sherbet, G. V. (Cancer Res. Unit, Univ. Dept. Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, England); Lakshmi, M. S. *Exp Cell Biol* 47(1): 61-70; 1979.

Differences in the surface components of 3T3 mouse fibroblasts and their simian virus 40-transformed counterparts were determined by isoelectric equilibrium analysis. The net negative surface charge density of the transformed cells appeared to be marginally lower than that of the untransformed cells. Studies in which the surface amino groups were modified with formaldehyde indicated that about 30% more cationic groups were present on the transformed cells; ie, the latter contain some additional basic material not detectable on the surface of normal cells. Ionization of the cationic groups in the transformed cells was inhibited by the strongly acidic carboxylic groups. This indicates that there is a distribution of extra cationic material in the vicinity of acidic glycoprotein components on the surface. The investigation also revealed that unidentified anionic groups that ionize at high pH are present on the transformed cells. The density of these groups, which appeared to be thiol groups, was 33% higher in the transformed cells than in the normal cells. (33 refs)

- 79-5221 The Emergence of Simian Virus 40 Variants in a Persistent Infection of Rhesus Monkey

Kidney Cells and Their Interaction with Standard Simian Virus 40. (Eng) Norkin, L. C. (Dept. Microbiology, Univ. Massachusetts, Amherst, MA 01003). *Virology* 95(2): 598-603; 1979.

The emergence of defective interfering (DI) variants of simian virus 40 (SV40) in LLC-MK₂ rhesus monkey kidney cells persistently infected with SV40 was studied. DI particles were first detected at 6 wk, were not detected at 7 and 8 wk, and were usually present from 9 wk on. DI particle production tended to parallel the number of cells producing plaque-forming units (PFU). Homologous interference by SV40 DI particles was not an all-or-none phenomenon and was the result of a competitive interaction with standard virus during replication. Preinfection with DI particle-containing stocks followed after 24 hr by superinfection with standard virus resulted in greater levels of interference than simultaneous coinfection, but there was no interference when cells were superinfected with carrier culture stock 24 hr after infection with standard virus. Most of the particles in the carrier culture stocks were not able to produce capsids (V antigen), the fraction of V-antigen-producing cells being somewhat reduced and the PFU yield being reduced by 20-fold in mixed infections. Coinfection of SV40 DI particle-infected cells with vesicular stomatitis virus (VSV) did not result in interference with VSV replication. Almost coincident with the emergence of DI particles, the population of standard large plaque virus was gradually replaced by virus which produced small, but equally cytopathic, virus. The uncloned carrier culture virus became temperature sensitive between 14 and 28 wk. There were changes in restriction endonuclease fragments of the carrier culture viral DNA by 2 wk, but most of the fragments were still indistinguishable from standard virus fragments at 57 wk. (22 refs)

79-5222 Intranuclear Particles in Keratoacanthoma: Possible Association with Malignant Degeneration. (Eng) Van De Staak, W. J. (Dept. Dermatology, Univ. Nijmegen, Javastraat 104, Nijmegen, Netherlands); Bergers, A. M. *Dermatologica* 158(6): 413-416; 1979.

An electron microscope investigation of keratoacanthomas from 12 patients is reported. Intranuclear viruslike particles (400-800 nanometers) were seen in three cases; two of these subsequently underwent malignant transformation to squamous cell carcinomas. These findings suggest that it is particularly important to exclude the possibility of malignant change in those tumors containing intranuclear particles. (12 refs)

79-5223 Intracisternal A Particles in Preimplantation Embryos of Feral Mice (*Mus musculus*). (Eng) Calarco, P. G. (Dept. Anatomy, Univ. California, San Francisco, CA 94143). *Intervirology* 11(6): 321-325; 1979.

Preimplantation embryos of feral mice (*Mus musculus*) were examined for expression of intracisternal A particles (IAP) using electron microscopy. IAP were not observed in zygotes, but at the two-cell stage large numbers of IAP were seen budding into the endoplasmic reticulum (ER), and a morphology characteristic of the very early stages of IAP formation was observed. Small amounts of crystalloid material were first seen at the two-cell stage. At the four- and eight-cell and morula stages there was a dramatic decrease in IAP with no apparent areas of budding IAP. There appeared to be more crystalloid material at these later stages. Very few IAP were seen within the ER at the blastocyst stage. At all stages the IAP had an outer shell diameter of approx 70 nanometers (nm) and an inner shell diameter of approx 33 nm. (23 refs)

79-5224 Use of the Transfection Assay to Detect Virus-specific Information in Human Tumor DNA. (Rus) Kniazev, P. G. (Lab. Biochemistry, Petrov Res. Inst. Oncology, Leningrad, USSR); Perevozchikov, A. P.; Korobitsyn, L. P.; Zhudina, A. I.; Kuznetsov, O. K.; Savost'ianov, G. A.; Diad'kova, A. M.; Seits, I. F. *Vopr Onkol* 25(5): 50-55; 1979.

An attempt was made to determine whether the DNA from human tumors contains virus-specific information. DNA specimens were isolated from the blood of a patient with myeloid leukemia (ML) and from specimens of pleomorphic cell rhabdomyosarcoma, synovial sarcoma, and neurinoma. The DNA specimens were then used to transfect diploid human embryo lung (HEL) cells; oncornavirus replication was determined by the radioisotope method. Of 10 cultures of HEL cells infected with DNA from the peripheral blood of the ML patient, 2 started to produce RNA-containing particles with a buoyant density of 1.16-1.18 g/ml. A sediment of the cultures that produced these particles showed reverse transcriptase activity. Electron microscope examination of culture fluid specimens from the 1.16- to 1.18-g/ml zone did not show particles typical of C-type oncornaviruses. The rhabdomyosarcoma, synovial sarcoma, and neurinoma specimens increased the proliferative activity of the HEL cells, but they did not produce viruslike particles. (11 refs)

79-5225 Nonrandom Correlation Between Selective Distribution of Virogenic 5-Bromodeoxyuridine and DNA-binding Nonhistone Proteins in Rat DNA. (Eng) Schwartz, S. A. (Dept. Pathology, Univ. Chicago, Chicago, IL 60637). *Exp Cell Biol* 47(3): 172-182; 1979.

In an attempt to elucidate further the molecular mechanism involved in the bromodeoxyuridine (BUdR)-mediated activation of endogenous C-type virus from normal rat embryo cells, nonhistone nuclear protein-DNA interactions

were analyzed in vitro. Native and kinetically fractionated DNA samples previously labeled with either [³H]-thymidine or [³H]-BUdR were combined with DNA-binding nonhistones and characterized according to isotope distribution and extent and localization of protein-binding sites. As in previous studies, [³H]-BUdR was relatively more concentrated in repetitive DNA, compared with [³H]-thymidine. In a membrane filter retention assay, nearly 60% of complete, 37% of repetitive, and 12% of nonrepeated DNA-protein reconstituted complexes were retained on the filters regardless of the isotopic precursor. However, a proportionately greater amount of [³H]-BUdR than [³H]-thymidine was recovered following extensive digestion of renatured complexes with DNase I, even though comparable amounts of DNA were acid-insoluble. The disproportionate binding of nonhistones to repetitive DNA, especially BUdR-substituted regions, may be related to the highly specific, well-characterized modifications in eukaryotic transcription attributed to the analog. (31 refs)

- 79-5226 Search for a New Antigen Associated with Oncornavirus D in Human Breast Cancer Cells. (Rus) Kosiakov, P. N. (D. I. Ivanovskii Inst. Virology, Moscow, USSR); Korosteleva, V. S.; Pavliuchenkova, R. P.; Kosiakova, N. P.; Nabokov, Iu. S.; Mogilevskii, I. L.; Kulakova, A. M. *Vopr Virusol* (3): 247-251; 1979.

This study was designed to verify whether the tissue of human benign and malignant breast tumors contains antigens associated with oncornavirus D. Surgical specimens obtained from 54 patients with breast cancer and 17 patients with benign breast lesions (8 fibroadenomas and 9 mastopathies) were assayed by a complement-fixation reaction using rabbit antisera to oncornavirus D-associated antigens extracted from tissue cultures of human malignant I-96 or HEP-2 cells. The antigen was detected in 9/54 breast cancer specimens at a titer of 1:80-1:160, compared with 1:1,280-1:2,560 in HEP-2 or I-96 cells; all 17 specimens of benign lesions were free of antigen. (13 refs)

- 79-5227 Intracellular Sodium and Potassium Concentrations and the Regulation of Gene Expression in Lytic Virus-infected and Virus-transformed Chick Cells. (Eng) Garry, R. F. (Univ. Texas, Austin, TX). *Diss Abstr Int [B]* 39(11): 5238-5239; 1979 (no refs)

- 79-5228 Antiviral Antibody Reacting on the Plasma Membrane Alters Measles Virus Expression Inside the Cell. (Eng) Fujinami, R. S. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Oldstone, M. B. *Nature* 279(5713): 529-530; 1979.

Experiments demonstrating that measles virus antibodies added to virus-infected HeLa cells decrease the amount of both viral structural polypeptide hemolysin expressed on the cell surface and a structural polypeptide (measles virus phosphoprotein) found inside the cell are presented. These observations indicate that antibody directed against an antigen on the cell surface can interfere with viral proteins expressed inside the cell. (18 refs)

- 79-5229 Reconstitution of Membranes with Individual Paramyxovirus Glycoproteins and Phospholipid in Chololate Solution. (Eng) Hsu, M. C. (Rockefeller Univ., New York, NY 10021); Scheid, A.; Choppin, P. W. *Virology* 95(2): 476-491; 1979.

A method for reconstituting biologically active membranes with individual Sendai virus glycoproteins (HN and F) and phosphatidylcholine is described. The glycoproteins were isolated in the presence of Triton X-100 and transferred into chololate soln by sedimentation into a sucrose gradient containing 2% chololate. The membranes were then reconstituted with HN or F and phosphatidylcholine by removal of the chololate through the use of dialysis. Experiments with radioactively labeled detergents showed that the removal of Triton X-100 by sedimentation into chololate and the removal of chololate by dialysis were essentially complete. With the F protein, vesicles 400-800 Å in diameter and filaments 600-800 Å long were formed, depending on the proportions of lipid and protein in the initial mixture. Both structures were covered with glycoprotein spikes. With the HN protein, only vesicles were formed, and the densities of the spikes on the surface were dependent on the initial lipid to protein ratio. Membranes reconstituted from HN protein exhibited hemagglutinating and neuraminidase activities. Reconstituted particles containing the F protein exhibited hemolytic activity when a mechanism was provided to attach the F protein-lipid complex to the cell; ie, by the addition of wheat germ agglutinin. These results confirm the role of F protein in membrane fusion and show that the requirements for F protein activity are the previously demonstrated proteolytic processing of F, the insertion of F protein into lipid, and the presence of an attachment mechanism. (33 refs)

- 79-5230 Use of UV Irradiation to Identify the Genetic Information of Vesicular Stomatitis Virus Responsible for Shutting Off Cellular RNA Synthesis. (Eng) Weck, P. K. (Dept. Microbiology, Univ. Virginia Sch. Medicine, Charlottesville, VA 22908); Carroll, A. R.; Shattuck, D. M.; Wagner, R. R. *J Virol* 30(3): 746-753; 1979.

The involvement of viral RNA and protein synthesis in the inhibition of host RNA metabolism was examined. UV irradiation of infectious vesicular stomatitis virus (VSV) was

employed to study the relationship between the expression of certain viral gene functions and viral inhibition of RNA synthesis in mouse myeloma (MPC-11) cells. Viral infectivity, protein synthesis, and viral messenger RNA synthesis were all highly susceptible to inactivation by UV radiation; however, low levels of viral transcriptase activity were detected in vitro in virus preparations subjected to large doses of UV radiation. In sharp contrast, the capacity of VSV to shut off cellular transcription was quite resistant to UV radiation. The data indicate that viral transcription is essential for the inhibition of host RNA metabolism, even though the synthesis of viral polypeptides in the inhibited cells could not be detected. At levels of UV radiation that inactivated all viral gene functions, except viral inhibition of cellular RNA synthesis, the only viral product detected was nonadenylated, low-mol-wt RNA species. (20 refs)

- 79-5231 Recovery of Three Distinct Biologically Active Type C Viruses from Cloned C57Bl/6 Melanoma Cells. (Eng) Levy, J. A. (Cancer Res. Inst., Univ. California Sch. Medicine, San Francisco, California 94143); Rutledge, F.; Dimpfl, J.; Silagi, S. *J Gen Virol* 43(2): 283-288; 1979.

The B16 C57Bl/6 melanoma cell line was cloned, and the 25 clones obtained were examined for melanin and virus production. One clone, 20282 E-7, that produced substantial amounts of melanin but no infectious virus, was selected, treated with 30 µg/ml iododeoxyuridine (IdUrd), and then cultured alone or overlaid with either NIH-ME, BALB-ME, human foreskin, or mink lung cells. Control cells of this clone, not treated with IdUrd, were cultured in the same manner. After weekly passages for 3 wk, the cells were examined for ecotropic and xenotropic virus production. Control cultures did not release ecotropic or xenotropic viruses. IdUrd-treated cells cultured alone produced a B-tropic virus, as determined by its preference for BALB-ME cells. Supernatants from IdUrd-treated cells cocultivated with NIH-ME cells were inoculated at different dilutions onto fresh NIH-ME cells every 7 days for 2-3 wk, which resulted in the isolation of a pure N-tropic virus that grew preferentially in NIH-ME cells and could not be passed through BALB/c-ME cells. From this same melanoma clone, a B-tropic virus free of N-tropic virus was obtained by selectively inoculating the supernatant from IdUrd-treated cells onto BALB-ME cells for several passages. A xenotropic murine leukemia virus (MuLV) was also isolated by treating the clone cells with IdUrd and cocultivating them with mink lung cells for four passages. Upon cocultivation with NRK-Harvey cells, the mink cells yielded a xenotropic virus pseudotype of murine sarcoma virus. Evidence of the X-tropic virus envelope was demonstrated by specific neutralization with rabbit anti-X-tropic virus antiserum and normal mouse sera. These same cells, if treated with IdUrd, produced a B-tropic virus.

After seven passages, the melanoma clone produced the B-tropic virus spontaneously but not the xenotropic virus. At this time, the cells were less pigmented than the nonvirus producing parental cell line. IdUrd-induced virus production in melanoma cells was accompanied by a reduction in melanin production. Puromycin and cycloheximide treatment of melanoma cells decreased melanin production to a lesser extent than did IdUrd treatment. Acute infection of the non-virus-producing melanoma cells by ecotropic MuLV caused a noticeable decrease in melanin production concomitant with virus replication in the cells. These findings confirm earlier reports that MuLV production by differentiated melanoma cells is associated with a decrease in melanin production. (21 refs)

- 79-5232 Neuroblastoma Cell Fusion by a Temperature-sensitive Mutant of Vesicular Stomatitis Virus. (Eng) Hughes, J. V. (Div. Biology, Kansas State Univ., Manhattan, KS 66506); Dille, B. J.; Thimmig, R. L.; Johnson, T. C.; Rabinowitz, S. G.; Dal Canto, M. C. *J Virol* 30(3): 883-890; 1979.

Data concerning the fusion of neuroblastoma cells by a temperature-sensitive mutant of vesicular stomatitis virus (*ts*G31) that does not mature properly when grown at 39 C are presented. *ts*G31 promoted extensive fusion of murine neuroblastoma cells at this nonpermissive temperature. Polykaryocytes (PKC's) apparently formed as a result of fusion from within the cells, which requires low doses of infectious virions for its promotion and is dependent on viral protein synthesis. Although 90% of infected N-18 neuroblastoma cells were fused by 15 hr after infection, larger PKC's continued to form, leading to an av of 28 nuclei per PKC as a result of PKC's fusing to each other. Two neuroblastoma cell lines underwent fusion, whereas three other cell lines (BHK-21, CHO, and 3T3) were incapable of forming PKC's, suggesting that nervous system-derived cells are particularly susceptible to vesicular stomatitis virus-induced fusion. Although the normal assembly of the protein components of this virus was deficient at 39 C, the G glycoprotein was inserted into the infected cell membranes at this temperature. Two lines of evidence suggest that the expression of G at the cell surface promotes this PKC formation: (1) inhibition of glycosylation, which may be involved in the migration of the G protein to the cellular plasma membranes, inhibits cell fusion; (2) addition of antiserum directed toward the purified G glycoprotein also inhibits cell fusion. (28 refs)

- 79-5233 Carcinoma of the Vulva Arising in Condylomata Acuminata. (Eng) Shafeek, M. A. (49 Giza St., Giza, Cairo, Egypt); Osman, M. I.; Hussein, M. A. *Obstet Gynecol* 54(1): 120-123; 1979.

The case of a 30-yr-old woman with a squamous cell carcinoma of the vulva arising in condylomata acuminata is presented. The patient was much younger than most patients with vulvar carcinomas. The vulvar growth was first noted during pregnancy, and it continued to grow and enlarge following delivery. Malignancy appeared to develop after a relatively short time. It is sometimes difficult to distinguish vulvar condylomata acuminata from carcinoma on the basis of clinical evidence alone. It is, therefore, mandatory in doubtful cases to take multiple biopsies from the lesion before treatment is instituted. (15 refs)

See also:

*(Rev.): 79-4815, 79-4853, 79-4866, 79-4867, 79-4868, 79-4869, 79-4870, 79-4871, 79-4872, 79-4873, 79-4874, 79-4875, 79-4876, 79-4877, 79-4878, 79-4879, 79-4880, 79-4881, 79-4882, 79-4883, 79-4884, 79-4885, 79-4886, 79-4887, 79-4888, 79-4889, 79-4890, 79-4891, 79-4892, 79-4893, 79-4894, 79-4895, 79-4896, 79-4897, 79-4898, 79-4902.

*(Chem.): 79-4943, 79-4952.

*(Immun.): 79-5236.

IMMUNOLOGY

79-5234 Some Perspectives on the Transfer of Cell-mediated Immunity by Immune-RNA. (Eng)

Dray, S. (Dept. Microbiology and Immunology, Univ. Illinois at Medical Center, 835 S. Wolcott, Chicago, IL 60612); Braun, D. P. *Mol Cell Biochem* 25(1): 15-31; 1979.

RNA extracts of lymphoid cells from immune hosts, including humans, monkeys, guinea pigs, and mice, were used to transfer in vivo and in vitro cell-mediated immune reactivity to a variety of antigens. The in vivo immune responses transferred by RNA included the delayed cutaneous hypersensitivity reaction to fungal and chemically defined antigens and the tumor-rejection reaction to guinea pig hepatoma antigens. The in vitro immune responses transferred by RNA included macrophage migration inhibition by fungal, chemically defined, and tumor antigens. The transfer activity of the RNA preparations was contained in the 8S to 18S species of RNA, and it was sensitive to RNase but not to DNase or trypsin. Antigen was not detectable in the RNA preparations, and it appeared to have no role in the transfer activity. Syngeneic, allogeneic, or xenogeneic sources of RNA could transfer immune reactivity. In each system tested, the transfer of cell-mediated reactivity by RNA was specific for the antigen used to sensitize the RNA donor. Prospects for the further application of immune RNA are explored. (68 refs)

79-5235 Immunological Resistance to Growth of Tumours in Syngeneic Multiparous Mice. (Eng)

Chandradasa, K. D. (Dept. Immunology, Univ. Liverpool, Liverpool, England); Barnes, R. M. *Eur J Cancer* 15(5): 671-677; 1979.

Investigations were undertaken to seek direct evidence for an immunological link between the experience of pregnancy and tumor rejection in mice. The hypothesis that BALB/c mice that have experienced a pregnancy are rendered immune to a 3-methylcholanthrene-induced syngeneic tumor (MC677) was tested by direct tumor cell challenge of multiparous mice and by cell-transfer assays using purified T cells obtained from the spleens of multiparous mice. Controls were virgin BALB/c mice of the same age. The results showed that mice that had experienced a single multiparous pregnancy were resistant to the growth of MC677. In addition, purified splenic T cells from multiparous mice inhibited tumor growth following implantation of a mixture of tumor cells and splenic T cells into normal recipient mice. Age-matched virgin controls

did not show resistance to tumor growth following challenge, and their lymphoid cells were not inhibitory to tumor cells. These results demonstrate clearly that pregnancy in mice confers a degree of transplantation resistance against syngeneic tumors, and they suggest that certain membrane-expressed oncofetal antigens are operative in tumor resistance. They also provide support for a possible immunological link between a decreased risk of breast cancer and early pregnancy in humans. (17 refs)

79-5236 Tumour Production by HSV-2 Transformed Lines in Rats and the Varying Response to Immunosuppression. (Eng) Macnab, J. C. (MRC Virology Unit, Inst. Virology, Church St., Glasgow G11 5JR, Scotland). *J Gen Virol* 43(part 1): 39-56; 1979.

Rat embryo cells transformed by two temperature-sensitive (*ts*) mutants of herpes simplex virus (HSV)-2 strain HG 52 and also by ultraviolet-irradiated HSV-2 strain 333 were inoculated into highly inbred host rats, which were either newborn or had undergone various immunosuppressive treatments. The latent period before a palpable tumor (a fibrosarcoma) was detected varied directly with the degree of immunosuppression of the host. Transformed cells could form tumors after a latent period of nearly 2 yr. All tumors were invasive and in some cases metastatic. The continuing expression of HSV information in 10 tumor cell lines was demonstrated by perinuclear and cytoplasmic staining in immunofluorescence studies using a rat antiserum directed against the early polypeptides of HSV-2 HG 52 infection and a rabbit serum prepared against a 24 hr cell infection with HSV-2 HG 52 *ts* 1. Sera from tumor-bearing rats fluoresced the surface of unfixed human or rat embryo cells 4-5 hr after infection with HSV-2 HG 52. In addition, the rabbit antiserum (4740 or 4741) fluoresced the surface of 80% of the tumor cells in culture. After 20 passages in vitro, transplanted tumors taking up to a year to form a tumor in a host rat also showed specific HSV cytoplasmic and perinuclear fluorescence in tests with the rat antiserum directed against early polypeptides of HSV-2 lytic infection. (28 refs)

79-5237 Effect of Rabbit Strain on Activity Level and Cytotoxicity of Serum Complement. III. Comparison of Four Tumor Target Cells. (Eng) Fox, R. R. (Jackson Lab., Bar Harbor, ME 04609); Cherry, M.; Shultz, K. L.; Salvatore, K. J. *J Hered* 70(2): 109-114; 1979.

The effects of rabbit strain on the activity and cytotoxicity of serum complement were determined in several murine tumor cell test systems, and the results were compared with those obtained previously using lymph node cells. Serum samples from 10 males and 10 females from each of 15 genetically defined strains of rabbits and from one hybrid were tested as sources of complement for the microtiter lymphocytotoxicity test using SaI-A, 6C3HED-A, BW5147, and L cells as target cells. The tumor cells were tested with appropriate H-2 antisera. Strain differences were particularly evident when the target cells were 6C3HED-A or L cells. BW5147 cells worked well with complement from most rabbit strains, but SAI-A cells were extremely refractory and few, if any, strains provided a good source for this test system. Rabbit strains IIIC/J, IIIVO/J, and the F₁ hybrid between them were among the six best strains when tested against the tumor cells and against the lymph node cells. Strain WH/J which carries the gene (*ha*) for hereditary lymphosarcoma, proved to be a good complement source with SaI-A and 6C3HED-A, both sarcomatous in nature. However, it was not a good complement source with BW5147, a lymphatic leukemia, or L cells. This is possible evidence for the presence of a common tumor antigen associated with lymphosarcoma in both the mouse and the rabbit. (19 refs)

- 79-5238 Structural Evidence for Independent Joining Region Gene in Immunoglobulin Heavy Chains from Anti-galactan Myeloma Proteins and its Potential Role in Generating Diversity in Complementarity-determining Regions. (Eng) Rao, D. N. (Lab. Cell Biology, NCI, Bethesda, MD 20205); Rudikoff, S.; Kruttsch, H.; Potter, M. *Proc Natl Acad Sci USA* 76(6): 2890-2894; 1979.

The variable region sequences of four heavy chains from $\beta(1-6)$ D-galactan-binding myeloma proteins were determined. Two of these proteins are identical to position 100, which is located in the third complementarity-determining region (CDR-3). The remaining two differ at a total of eight positions over the first 100 amino acids, and all of the differences can be explained by single-base mutations at the DNA level. When an assessment is made of the protein segment following CDR-3, which has been termed "J segment" or "FR4," a completely different pattern of variation is observed. The J segments from the four proteins can be divided into two sets. Members of each set share a series of linked amino acids not found in members of the alternative set. The two proteins identical to position 100 have J segments from the two different sets, suggesting that recombination has occurred between *V* and *J* genes. An examination of the CDR-3 sequences from the four heavy chains revealed substitutions at positions 100 and 105. Gly is found at 100 in two of the proteins and His in the remaining two. In the two proteins with Gly-100, the following J sequence is limited to one of the two sets of J segments defined by linked amino acids. Similarly, the two heavy

chains with His-100 have J segments from the second set. Thus, at the protein level, an apparent association is seen between CDR-3 and the J segment. If CDR-3 should be found linked to the J segment at the DNA level, a new mechanism would be introduced for increasing antibody diversity by recombining various *CDR-3* plus *J* genes with genes coding for the remainder of the variable region. Alternatively, if CDR-3 were coded for by the *V* gene, then the recombination of *V* with *J* may provide an opportunity to introduce mutations in *CDR-3*. In this case, the linkage of amino acids in CDR-3 and the J segments would suggest that recognition signals are used such that certain *V* genes only pair with a given *J* gene. (23 refs)

- 79-5239 A Multi-faceted Approach to Characterization and Isolation of Immune Complexes. (Eng) Morgan, A. C. (Baylor Coll. Medicine, Houston, TX); Rossen, R. D.; Challand, B. J.; Twomey, J. J.; Hersh, E. M. *Protides Biol Fluid Proc Colloq* 26: 131-136; 1978.

An attempt was made to identify tumor-reactive antibodies and other proteins present in 2.7% polyethylene glycol precipitates obtained from selected cancer patients and normal controls. Sera from patients with malignant melanoma and colon cancer contained 12S-19S complexes that, when dissociated at pH 2.9, released proteins that sedimented at 3.0S-5.0S and bound specifically to cultured tumor cells. Sera from most normal donors contained 25S complexes that were dissociated by affinity chromatography on heat-aggregated IgG-Sepharose into a 7S IgG cytotoxin that was reactive with malignant melanoma cells and an antiglobulin that blocked the antigen-combining activity of the cytotoxin. Thus, soluble immune complexes may be found in the sera of both cancer patients and normal donors. In the complexes from the cancer patients, however, the immunoglobulin in the complex may have undergone partial proteolysis before or during characterization. (15 refs)

- 79-5240 Milk Precipitins and Circulating Immune Complexes in Selective IgA Deficiency. (Eng) Cunningham-Rundles, C. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Brandeis, W. E.; Good, R. A.; Day, N. K. *Protides Biol Fluid Proc Colloq* 26: 137-140; 1978.

Milk precipitins and circulating immune complexes were investigated in 15 patients with selective IgA deficiency and 7 patients with malignancies and IgA deficiencies. Thirteen of the 22 patients had circulating immune complexes and 11/22 had milk precipitins. No patient had milk precipitins and a negative test for immune complexes. A serum sample drawn from a patient 60 min after he drank milk contained casein. The low level of immune complexes initially detected disappeared by 60 min and then reappeared, to

reach a max at 120 min. There were no significant changes in serum levels of total complement, C3, or C1q after the milk was consumed. It is possible that the complexed antigen in the circulations of these patients was a milk protein. (8 refs)

- 79-5241 Interferon in the Replication of Herpes Simplex Virus in Normal and Pathological Nerve Cells. (Eng) de la Pena, N. C. (Res. Dept. Inst. Oncology Angel H. Roffo, Buenos Aires Univ., Buenos Aires, Argentina); Bal, E.; Puricelli, L.; Diaz, A.; De Lustig, E. S. *IARC Sci Publ* 24(11): 1055-1066; 1978.

The role of human interferon (HI) and human colostrum secretory IgA (S-IgA) in herpes simplex virus (HSV) replication in the nervous system was studied in vitro. When trigeminal ganglia explants from rabbits with experimental herpetic keratitis were infected with HSV type 1 (HSV-1) and treated topically with HI or HI/S-IgA, HSV was recovered from 30% of the ganglia after 15-19 days cocultivation on rabbit kidney (RK 13) cells. A restrictive HSV productive infection was demonstrated in ganglia and nerves of newborn rabbits in organ culture, the yields always being higher in nerve cultures. HI had no direct effect on HSV-1 replication. However, when explants were treated with HI and IgG for 48 hr before and after infection, a delay in the expression of HSV-1 was detected by cocultivation. HSV-1 and HSV-2 replicated in a C1300 murine neuroblastoma clone, the cytopathic effects being more marked for HSV-2 at 24 hr. HSV-specific antigens were demonstrated by the immunoperoxidase technique. (11 refs)

- 79-5242 Carcinoembryonic Antigen (CEA) and CEA-like Activity in Ascites and Pleural Effusions. (Ger) Eimermacher, H. (Medizinische Universitätsklinik, Ruhruniversität Bochum, D-4630 Bochum, W. Germany); Tinnefeld, W.; Pressler, H.; Schuster, P.; Beyer, H. K. *Klin Wochenschr* 57(11): 575-579; 1979.

Carcinoembryonic antigen (CEA) levels were studied in nonmalignant ascites and pleural effusions from 18 patients with cardiac insufficiency pneumonia or liver cirrhosis and in malignant effusions from 21 patients with renal cell carcinoma or tumors of the liver, lungs, breast, stomach, uterine cervix, ovaries, and esophagus. Increased CEA activity (>2.5 nanograms/ml) was found in 1/18 benign effusions and in 12/21 malignant effusions. The correlation between CEA levels in serum and effusions was studied in 20 tumor patients: the serum CEA titers were elevated in 9/12 patients with elevated effusion titers and were normal in the 3 others. The serum CEA titer was also increased in 1/8 patients with a normal CEA effusion titer. The considerable discrepancy between the CEA levels in

the sera and effusions of the tumor patients shows that the tumor antigens are actively secreted by the tumor cells rather than simply released from the blood. (18 refs)

- 79-5243 Expression of "Ia-like" Antigens on Cells from a Human Endometrial Carcinoma Cell Line, END-1. (Eng) Carrel, S. (Unit Human Cancer Immunology, Lausanne Branch, Ludwig Inst. Cancer Res., 1066 Epalinges, s/Lausanne, Switzerland); Gross, N.; Heumann, D.; Mach, J. P. *Transplantation* 27(6): 431-433; 1979.

Evidence is presented that cells from a long-term human endometrial carcinoma cell line, END-1, express immune-associated (Ia)-like antigens, as assessed by complement-dependent lysis and by immunofluorescence using rabbit antiserum against Ia-like antigens. The presence of the antigens on the END-1 cells was confirmed by immunochemical demonstration of 28,000- and 33,000-mol wt components on the cell surface. (22 refs)

- 79-5244 Cell-mediated Cytotoxicity Engendered by IB-G-Region Determinants of the H-2 Complex. Absence of H-2K and D Restriction. (Eng) Wolf, S. J. (Immunobiology Res. Unit, Dept. Pathology, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA); Elkins, W. L. *Immunogenetics* 8(2): 171-175; 1979.

The congeneric strains C57BL/10.A (4R) and (2R) differ in the central regions of the H-2 complex (IB-G segment). It is shown that one or more antigens encoded in the H-2 IB-G segment of the 2R genome stimulate 4R lymphocytes to give a strong cytotoxic response against P815 mastocytoma cell targets. The P815 tumor cells were obtained from the ascites fluid of serially transplanted DBA/2 mice. Single-cell suspensions provided 5×10^6 viable responder cells that were then cocultivated with 5×10^6 stimulator cells (previously inactivated by 2,500 R from a ^{137}Cs source). After incubation of the cultures for 5 days in humidified CO_2 at 37 C, killer cells were generated. Unstimulated or concanavalin A (Con A)-stimulated spleen cells provided the lymphoid target cells. The target cells were labeled with ^{51}Cr -sodium chromate. The results demonstrate that 4R anti-2R killers can be readily detected when P815 target cells are used. The killing of labeled P815 cells was inhibited equally well by unlabeled 2R lymphoblasts and P815. Since P815 and strain 2R share IC-G alleles derived from the H-2d chromosome, this genetic difference may be the source of the antigens recognized. The killing is not restricted by the H-2K or H-2D alleles, since P815 and strain 2R do not share these alleles. In one-third of the trials, the response to putative IC-G region antigens was approx as strong as that to H-2D antigens on the mastocytoma. (10 refs)

- 79-5245 Functional Separation In Vivo of Both Antigens Encoded by H-2 Subregion and Non-H-2 Loci. (Eng) Wolters, E. A. (Dept. Cell Biology and Genetics, Erasmus Univ., P.O. Box 1738, Rotterdam, Netherlands); Benner, R. *Nature* 279(5714): 642-643; 1979.

A delayed-type hypersensitivity (DHT) assay was developed to measure the occurrence of T-effector cells after in vivo immunization with different histocompatibility antigens. The DTH T-effector cells generated in graft vs host (GvH) and host vs graft reactions are specific for largely different sets of histocompatibility antigens, with selective stimulation by H-2I- and I-locus antigens under GvH conditions. (15 refs)

- 79-5246 Source of Tumor Cells Influences Their Immune Recognition by H-2-matched Mice. (Eng) Forni, G. (Inst. Microbiology, Univ. Torino, Via Santena 9, 10126 Turin, Italy); Varesio, L.; Giovarelli, M.; Landolfo, S. *Transplantation* 27(6): 433-435; 1979.

The presence of an appropriate WBC population enhanced the immune recognition of proliferating tumor cells in H-2 matched hosts, and it brought about the rejection of an otherwise lethal inoculum. DBA/2 mice challenged with ADK-1t adenocarcinoma cells of BALB/c origin (spontaneous) recognized minor alloantigens displayed by the tumor cells, but the immune reaction was not enough to block tumor proliferation. When inactivated BALB/c macrophages or B lymphocytes were mixed with the tumor cells, the tumor was rejected. (19 refs)

- 79-5247 HLA Compatibility in Couples with Children Suffering from Acute Leukemia or Aplastic Anemia. (Eng) Werner-Favre, C. (Transplantation Immunology Unit, Hopital Cantonal, 1211 Geneva 4, Switzerland); Jeannet, M. *Tissue Antigens Histocompat Immunogenet* 13(4): 307-309; 1979.

The frequency of common HLA-A and -B antigens was determined in 30 couples with a child with acute leukemia (AL), 34 couples with a child with aplastic anemia (AA), and 58 random couples with healthy children. The number of couples sharing at least two common antigens was increased among parents of children with AL and AA (30% and 26%, respectively, vs 8% of the couples with healthy children). (8 refs)

- 79-5248 Absence of Four H-2d Antigenic Specificities in an H-2d Sarcoma. (Eng) Garrido, F. (Tumour Immunology Unit, Facultad de Medicina,

Granada, Spain); Perez, M.; Torres, M. D. *J Immunogenet* 6(2): 83-86; 1979.

A BALB/c sarcoma, MCG4, induced as a solid tumor with 0.2 mg of methylcholanthrene, was serially transplanted sc in syngeneic mice. The ascites form obtained was used to study the expression of H-2 antigenic specificities in a postlabeling radioassay. MCG4 did not express H-2D.4 (private specificity of H-2d haplotypes) or H-2.3, H-2.8, and H-2.13 (public specificities). However, it did express H-2.5 (a public specificity not present in H-2d cells). These results were confirmed by quantitative absorption analysis using MCG4 and positive-negative normal lymphoid cells for a particular specificity. The expression of H-2 antigens may be controlled by regulatory genes. (14 refs)

- 79-5249 Possible Association Between HLA-AW24 and Metastatic Testicular Germ-Cell Tumours (Letter to Editor). (Eng) Carr, B. I. (Wisconsin Clinical Cancer Center, Madison, WI 53706); Bach, F. H. *Lancet* 1(8130): 1346-1347; 1979.

The possible association between HLA-A locus A antigen W24 and testicular germ-cell tumors was studied in 20 patients with testicular teratocarcinoma (9 with distant metastases). A total of 5/20 (25%) patients possessed the AW-24 antigen; all five had distant metastases (55%). The frequency of AW-24 in patients with metastatic tumors is significantly higher than the normal frequency (16%) in North American Whites ($P = 0.0075$) and than the frequency in the non-metastatic group ($P = 0.008$). It is suggested that the presence of the AW-24 antigen might indicate an increased likelihood of distant metastases in patients with non-seminomatous testicular germ-cell tumors. (13 refs)

- 79-5250 DNA-synthesizing T and Non-T Cells in Chronic Lymphocytic Leukemia. (Eng) van der Woerd-de Lange, J. A. (I. Medizinische Abteilung, Städtisches Krankenhaus Schwabing, Kolner Platz 1, D-8000 München 40, W. Germany); Dohrmann, J.; Huber, C.; Schick, P.; Rauert, K.; Begemann, H. *Blut* 37(6): 319-326; 1978.

In an effort to correlate the extent of blood lymphocyte proliferation with clinical parameters of underlying lymphoproliferative disease, the number of DNA-synthesizing peripheral blood lymphocytes in 21 patients with chronic lymphocytic leukemia (CLL) and in 8 hematologically normal persons was investigated autoradiographically. The lymphocytes were separated according to ability to form erythrocyte (E) rosettes into T and non-T lymphoid cells. There was a normal number of proliferating T lymphoid cells and an increased number of proliferating non-T lymphoid cells in clinical Stages 0-I. In Stages III-IV, there was a significant increase in the proliferation of both T and

non-T lymphoid cells. The data are compatible with, but do not prove, the view that blood lymphocyte proliferation in CLL is primarily a feature of the leukemic cells and that it correlates with the actual rate of production of the malignant cell clone. (20 refs)

- 79-5251 **Crawling Movements of Lymphocytes on and Beneath Fibroblasts in Culture.** (Eng) Chang, T. W. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA 02139); Celis, E.; Eisen, H. N.; Solomon, F. *Proc Natl Acad Sci USA* 76(6): 2917-2921; 1979.

An approach to the analysis of the exploratory and migratory behavior of lymphocytes is described. Mouse lymphocytes were stimulated immunologically in vivo or in vitro. When introduced into a culture of mouse 3T3 or L cells (fibroblasts) and followed by live-cell microscopy, some of these lymphocytes were observed (without a time-lapse device) to crawl on top of, along the edges of, and preferentially beneath the attached fibroblasts. The crawling rate was as rapid as 20 $\mu\text{m}/\text{min}$. The ability of the lymphocytes to penetrate beneath attached 3T3 cells (diagnostic of crawling activity) was examined under a variety of conditions. Crawling was inhibited almost completely by decreasing the incubation temperature from 37 to 20-25 C, partially by treating the cells with 10 mM NaN_3 , and completely by exposing the cells to cytochalasin B (10 $\mu\text{g}/\text{ml}$) or colchicine (50 μM). These agents or treatments either interrupt energy metabolism or disrupt the cytoskeleton. Crawling was partially inhibited by removing both Ca^{2+} and Mg^{2+} but not by removing Ca^{2+} alone. Crawling lymphocytes were virtually absent in normal thymus and spleen cells, but they were greatly increased in 5-day mixed lymphocyte cultures and in peritoneal exudate lymphocytes taken after mice had been immunized with allogeneic tumor cells. T cells accounted for most of the crawlers in the mixed lymphocyte cultures. Of two T-cell leukemia lines tested, R1+ cells were crawlers but EL-4 cells were not. The H-2 haplotype of the 3T3 fibroblasts (ie, syngeneic or allogeneic) had no apparent effect on lymphocyte crawling activity. It is suggested that the crawling behavior may be related to immune surveillance (the exploration of cell-surface antigens by lymphocytes), to the mode of action of cytotoxic T cells, to the migration of lymphocytes across blood vessel walls, or to the penetration of lymphocytes into solid masses of normal or tumor tissue. (20 refs)

- 79-5252 **Lymphocytes Subpopulation in Normal Family Members of Patients with Alpha-Chain Disease.** (Eng) Alsabti, E. A. (Flat No. 5, 8 Norfolk Terrace, Brighton BN1 3AD, England); Safo, M. H.; Shaheen, A. *J Surg Oncol* 11(4): 365-374; 1979.

Sera from normal family members of eight patients with alpha-chain disease and intestinal lymphoma were in-

vestigated by immunoelectrophoresis for abnormal alpha-chain proteins. Abnormal proteins were detected in 23 members of four families; all the positive cases were first-degree relatives. In these relatives and the lymphoma patients, the proportion of circulating B lymphocytes was much higher than normal and that of T lymphocytes was lower than normal. Surface immunofluorescence studies indicated that the percentage of IgA-bearing lymphocytes was increased in the patients and their relatives with abnormal alpha-chain patterns. Serum IgA levels were also above normal in the patients and their relatives. Neither the patients nor the relatives could be sensitized to dinitrochlorobenzene, and their tuberculin skin tests were negative. These results suggest that alpha-chain disease is a B-cell disease of the IgA type and that it is transmitted by a hereditary factor associated with depressed cellular immunity. (17 refs)

- 79-5253 **Level of 3-Oxyanthranilic Acid in the Urine of Patients with Urinary Bladder Cancer.** (Rus) Korosteleva, T. A. (Lab. Immunology Carcinogenesis, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Kliucharev, B. V.; Benteleva, T. A. *Vopr Onkol* 25(6): 36-39; 1979.

An immunological assay was developed to detect an antigen containing as a determinant 3-oxyanthranilic acid (3-OAA), in the urine of patients with urinary bladder cancer. Urine specimens from 38 patients (20 had papillary tumors and 18 had infiltrative tumors of the urinary bladder) were assayed in a double-diffusion reaction with rabbit antisera containing antibodies against 3-OAA. The antigen was present in 25/38 patient urine specimens, but it was absent from the urine of all 17 healthy controls. (8 refs)

- 79-5254 **Reduced Lymphocyte Stimulation as an Expression of Reduced Immunoreactivity in Cancer Patients.** (Ger) Heilmann, E. (Medizinischen Poliklinik der Westfälischen Wilhelms-Universität Münster, Münster, W. Germany); Sasse, W.; Berghaus, I. *Inn Med* 6(3): 94-98; 1979.

Mitogen stimulation of cultured peripheral blood lymphocytes from 87 cancer patients and 45 healthy controls was compared. All patients had undergone surgery 6-12 mo previously; none were given cytostatics, radiotherapy, or corticosteroids, except for 20 with breast carcinoma, who had finished radiotherapy >6 mo previously. The effects of pokeweed mitogen (PWM, 100 $\mu\text{g}/\text{ml}$), phytohemagglutinin (PHA, 0.5 $\mu\text{g}/\text{ml}$), concanavalin A (Con A, 100 $\mu\text{g}/\text{ml}$), and lipopolysaccharide (LPS, 50 $\mu\text{g}/\text{ml}$) were studied by measuring ^3H -thymidine (TdR) uptake after 72 hr of incubation with mitogen only and after 10 hr of incubation with TdR. After stimulation with PHA, PWM, or

Con A, the av TdR uptake was less than one-half of the control value for cells from 60 patients with gastrointestinal carcinoma and 20 women with breast carcinoma ($p < 0.01$). Uptake was higher in cells from all categories of patients after stimulation with LPS. In seven patients who had carcinoma of the papilla of Vater, uptake after the other three mitogens was similar to that of controls. Except for the breast cancer patients, the av uptake of the patients cells was higher ($p < 0.05$) than that of control cells if no mitogen was added. The unstimulated uptake of cells from breast cancer patients was close to the control value. The clinical significance of lymphocyte stimulation by mitogens cannot be ascertained without further study. (23 refs)

- 79-5255 Blastogenic Response of Spleen Cells from C1300 Neuroblastoma-bearing Mice to Tumor Cells or Soluble and Insoluble Tumor Antigens. (Eng) Sugimoto, T. (Dept. Pediatrics, Kyoto Prefectural Univ. Medicine, Hirokoji Kawaramachi, Kamigyo-ku, Kyoto 602, Japan); Sawada, T.; Tozawa, M.; Kusunoki, T.; Kishida, T. *Gann* 70(3): 327-336; 1979.

The blastogenic (BG) response of spleen cells from C1300 neuroblastoma-bearing A/J mice to tumor cells or soluble and insoluble tumor antigens was studied. Mice inoculated with 1×10^6 syngeneic neuroblastoma cells had a palpable tumor after 1 wk, and the tumor grew uniformly. A hypertonic KCl extract of the tumor induced a BC response in syngeneic spleen cells from tumor-bearing mice, and the tumor antigens were considered solubilized from the tumor cells by KCl. Soluble tumor antigens and insoluble tumor antigens attached to Sepharose 4B beads induced equal spleen cell BG activity. The BG activity of spleen cells to insoluble tumor antigens was less than one-third of that in the mixed lymphocyte-tumor cell reaction (MLTR) assays. The initial information of the BG response was transmitted to the responder cells without the entrance of tumor antigens into the cells, as shown by experiments using insoluble tumor antigens. BG responses to soluble tumor antigens and to irradiated tumor cells (MLTR) in spleen cells from tumor-bearing mice were serially assayed after tumor cell injection. The response to soluble tumor antigens reached a peak 2 wk after inoculation, but a progressive depression of the response was observed after marked tumor growth. Although the BG activity of soluble tumor antigens was small, changes in consecutive responses to soluble tumor antigens in tumor-bearing mice were well-correlated with those in the MLTR. The BG responses to soluble tumor antigens and MLTR were considered to be the manifestation of tumor-specific cell-mediated immunity. Furthermore, the serial BG responses to concanavalin A and lipopolysaccharide were also coincident with those of tumor-specific immunity. (27 refs)

- 79-5256 Effect of ALS or ATS Administration on Tumor Formation in Two-Stage Skin Carcinogenesis. (Eng) Stenback, F. (Dept. Pathology, Univ. Kuopio, Harjulantie 1, Kuopio, Finland); Curtis, G.; Ryan, W. *Cancer Immunol Immunother* 6(2): 125-128; 1979.

The effects of antilymphocyte serum (ALS) and antithymocyte serum (ATS) on two-stage skin carcinogenesis were determined in female Swiss mice. The mice were given a single dose of 9,10-dimethylbenz(a)anthracene (DMBA: 50 μ g) followed by twice weekly applications of 12-O-tetradecanoylphorbol-13-acetate (TPA) for 25 wk. Some of the mice were also given four injections of ALS or ATS (1.25 mg/100 g/injection) during initiation or promotion. When given during initiation, ATS increased the tumor incidence by 83%, increased the number of tumors/animal from 2.6 to 4.2, and decreased the latent period by 27%, compared with animals given DMBA/TPA alone. ATS had a less-pronounced effect when given during promotion: tumor incidence was increased by 50%, and the av number of tumors per animal was 3.1. When given during initiation, ALS increased the tumor incidence by 33%, and the av number of tumors/animal was 3.1. When ALS was given during promotion, the effect on tumor formation was negligible; ie, 52 tumors were observed in 21 animals, vs 48 tumors in 18 DMBA/TPA-treated animals. The types of tumors formed, their biological behavior, and their morphology were not markedly affected by ALS or ATS. Almost all tumors were benign papillomas. The results show an obvious enhancing effect of immunosuppressive treatment. ATS and, to a certain degree, ALS, may allow a larger number of potential neoplastic foci to grow and become manifest as visible tumors. During promotion, only a small number of latent cells are affected, causing a less obvious increase in tumor incidence. (26 refs)

- 79-5257 Pinocytic Activity and CSF Production of Macrophages During the Growth of the Lewis Lung Carcinoma in Mice. (Eng) Von Melchner, H. (Westdeutsches Tumorzentrum, Innere Universitätsklinik (Tumorforschung), Hufelandstr. 55, D-4300 Essen 1, W. Germany); Hilgard, P. *Eur J Cancer* 15(5): 779-783; 1979.

^{198}Au colloidal gold was used to record the pinocytic activity of peritoneal macrophages from C57BL mice bearing transplanted Lewis lung carcinomas. Although macrophage uptake of gold particles was depressed 3 days after tumor transplantation, nonspecific stimulation by thioglycolate increased their pinocytic activity above that of control macrophages. Ten days posttransplantation, macrophage gold uptake was still suppressed and the response to stimulation decreased. During the final stage of tumor growth (day 16), the macrophages appeared to be activated spontaneously since no additional uptake was

recorded after thioglycolate injection. An increase in blood clearance and splenic uptake of gold particles by tumor-bearing animals on days 13 and 16 correlated with the in vitro finding of macrophage stimulation during the final stage of tumor growth. The depression of pinocytic activity on day 10 was associated with a decrease in the production of macrophage colony-stimulating factor. (10 refs)

- 79-5258 Phospholipid Methylation in Macrophages Is Inhibited by Chemotactic Factors. (Eng) Pike, M. C. (Lab. Immune Effector Function, Howard Hughes Medical Inst., Duke Univ. Medical Center, Durham, NC 27710); Kredich, N. M.; Snyderman, R. *Proc Natl Acad Sci USA* 76(6): 2922-2926; 1979.

In an attempt to define the methylation requirement for chemotaxis, the effect of chemotactic factors (CF's) on protein carboxy-O-methylation and phospholipid (PL) methylation in male Hartley guinea pig macrophages was examined. Chemotactic agents tested over a wide dose and time range produced no alteration in carboxy-O-methylation. However, these agents did produce an effect on the methylation of phosphatidylethanolamine (PE) by macrophages. S-adenosyl-L-methionine-mediated PL methylation was inhibited by as much as 73% by CF's, and there was excellent correlation ($r = 0.99$) between their concentrations for producing half-max chemotactic responses and for inhibiting PL methylation. The inhibition of methylation by CF's was observed at all incubation times and could not be explained by an increased turnover of membrane PL. Neither the chemotaxis antagonist fPhe-Met nor the nonchemotactic tripeptide Met-Met-Met significantly depressed PL methylation. Immune phagocytosis by macrophages similarly did not alter PL methylation. The CF's produced no alteration in total macrophage PL synthesis or in PL methylation in a non-chemotactic cell type. The formation of newly methylated derivatives of PE in macrophages was decreased by a biologically active dose of CF. These findings indicate that CF's are capable of altering the methylation of PE in chemotactically responsive cells. The inhibition of PL methylation by CF's may be necessary for the translation of a chemotactic signal on the surface of the cell into directional cell movement. (20 refs)

- 79-5259 Rat Mutant (*nznu*) Showing "Nude" Characteristics. (Eng) Berridge, M. V. (Wellington Cancer and Medical Res. Inst., Clinical Sch. Medicine, Wellington, New Zealand); O'Kech, N.; McNeilage, L. J.; Heslop, B. F.; Moore, R. *Transplantation* 27(6): 410-413; 1979.

A new rat mutant (*nznu*) that shows characteristics similar to those of the nude mouse is described. The discovery of hairless rats in a colony of outbred albinos led to the

establishment of a conventionally maintained colony in which there is a predictable incidence of nude rats. The mutant is an autosomal recessive trait. The homozygotes are essentially hairless (except for stunted vibrissae) and they show deficient thymus gland development. Under conventional breeding conditions, the mutants are difficult to raise and few survive weaning. The absence of functional thymus-derived lymphocytes in the nude rat is implied by (1) an acceptance of histoincompatible skin grafts, (2) a lack of response to the T-cell mitogens phytohemagglutinin and concanavalin A, and (3) an absence of cells sensitive to alloantiserum directed against rat thymus-derived lymphocytes. Although total blood WBC from the nude rat were within the normal range, differential counting of WBC showed a 4-fold elevation of neutrophils and a 2.5-fold reduction of lymphocytes, compared with levels in normal rats. Phenotypically normal heterozygotes gave values intermediate between those of nude and normal rats. (17 refs)

- 79-5260 Spontaneous Tumors in Nude Mice: Effect of the Viable Yellow Gene. (Eng) Stutman, O. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). *Exp Cell Biol* 47(2): 129-135; 1979.

The incidence and type of spontaneous tumors in athymic nude (*nu/nu*) mice (partially inbred in a CBA/H background) that were also carrying the viable yellow gene (*A-vy*, derived from C57BL/6JA-*vy* mice) were comparable to those observed in the phenotypically normal *nu/+* and *+/+* control crosses carrying the *A-vy* gene. The *A-vy* gene increased the incidence of spontaneous and induced tumors in most mouse strains. These results argue against a role of thymus-dependent immunity as a possible control mechanism of tumor development. (23 refs)

- 79-5261 Cellular Tumorigenicity in Nude Mice: Test of Associations among Loss of Cell-Surface Fibronectin, Anchorage Independence, and Tumor-forming Ability. (Eng) Kahn, P. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, New York 10461); Shin, S. *J Cell Biol* 82(1): 1-16; 1979.

Fibronectin (FN; also called large external transformation-sensitive protein or cell-surface protein), a glycoprotein that is frequently absent or greatly reduced on the surface of malignant cells grown in vitro, may be a useful marker of cellular malignancy. Therefore, tests of the specific association among the degree of expression of FN, anchorage-independent cell growth, and tumorigenicity in athymic nude mice were carried out in a variety of diploid cell strains and established cell lines. When the presence of surface FN was assayed by indirect immunofluorescence using rabbit antisera against human cold insoluble globulin, rodent plasma FN, or chicken cell-surface FN,

tumorigenic cells often showed very low surface fluorescence although many highly tumorigenic fibroblast cell lines from several species stained strongly with all three antisera. Nontumorigenic cell lines almost always exhibited an extensive extracellular matrix of FN. When cells were assayed for the ability to form colonies in methylcellulose, anchorage-dependent and FN-positive phenotypes cosegregated and were the uniform phenotype in nontumorigenic cells, with the exception of three anchorage-independent human skin fibroblast lines, two of which were FN-positive and one FN-negative. While anchorage-independent and FN-negative phenotypes usually cosegregated in tumorigenic cells, they occasionally dissociated; and usually it was the anchorage-independent rather than FN-negative phenotype that cosegregated with tumorigenicity. When FN-positive but anchorage-independent cells were grown as tumors in nude mice and then reintroduced into culture, five of the six tumor-derived cell lines retained the same amount of surface FN. Hybrids between normal human diploid fibroblasts and the highly malignant mouse cell line A9 were mostly anchorage-independent, FN-positive, and tumorigenic in nude mice. These results indicate that the loss of cell-surface FN is not a necessary step in the process of malignant transformation and that the growth of FN-positive cells as tumors does not require a prior selection *in vivo* for FN-negative subpopulations. (65 refs)

- 79-5262** Immunochemical Characterization of Surface Antigens of TerC, a Teratocarcinoma-derived Cell Line. (Eng) Larraga, V. (Instituto de Immunologia y Biologia Microbiana, Velazquez 144, Madrid-6, Spain); Edidin, M. *Proc Natl Acad Sci USA* 76(6): 2912-2916; 1979.

Additional information on the biochemical characterization of antigens precipitated from surface-labeled TerC cells (derived from the mouse testicular teratoma 402AX) and from cross-reacting cl Id cells (derived from mouse L cells). Rabbit and mouse antisera prepared against 402AX cells precipitated both glycoproteins and glycolipids from detergent extracts of ¹²⁵I-labeled TerC cells. Extracts of immunoprecipitates with chloroform/methanol (2:1, (volume/volume)) were resolved on thin-layer gels into multiple peaks. More species were seen in extracts of TerC cells than in extracts of the cross-reacting cl Id cells. The teratocarcinoma antigens could be extracted out of chloroform/methanol into buffered saline. Incubation in these secondary extracts converted unreactive cells (lymphocytes) to cells reactive with antisera against the teratocarcinoma. Furthermore, the coated cells absorbed at least 80% of the activity of antisera against TerC target cells. (28 refs)

- 79-5263** Cell Surface Antigens of Human Melanoma Identified by Monoclonal Antibody. (Eng)

Yeh, M. Y. (Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Hellstrom, I.; Brown, J. P.; Warner, G. A.; Hansen, J. A.; Hellstrom, K. E. *Proc Natl Acad Sci USA* 76(6): 2927-2931; 1979.

Mouse NS-1 myeloma cells were fused with spleen cells from BALB/c mice that had been immunized with a short-term explant of a human melanoma (M1804). Hybrid cells were grown in selective medium and tested for the production of antibody to surface antigens of M1804 cells. Three hybrids produced antibodies that bound to the melanoma cells but not to autologous skin fibroblasts, and these hybrids were cloned. Antibodies produced by two of the clones were cytotoxic to M1804 cells in the presence of rabbit complement. Extensive specificity tests showed that the antibodies produced by the clones bound strongly only to M1804 cells; significant, although weaker, binding occurred with 2/11 allogeneic melanomas. Apart from weak binding of the antibody produced by one of the clones to a breast carcinoma, binding assays of 5 carcinomas, 1 sarcoma, and fibroblasts from 17 individuals were negative, as were cytotoxic tests of 10 lymphoblastoid cell lines and peripheral blood lymphocytes from 68 normal donors and 12 chronic lymphocytic leukemia patients. These results suggest that one or more determinants of a melanoma-associated antigen(s) whose expression is limited to a small proportion of melanomas were identified. (16 refs)

- 79-5264** Clonal Evolution of Myeloma Cells Leads to Quantitative Changes in Immunoglobulin Secretion and Surface Antigen Expression. (Eng) Lcibson, P. J. (La Rabida-Univ. Chicago Inst., Chicago, IL 60649); Loken, M. R.; Panem, S.; Schreiber, H. *Proc Natl Acad Sci USA* 76(6): 2937-2941; 1979.

The evolution of variants from a single well-differentiated myeloma cell was studied. A fresh clonal isolate of S107 myeloma cells possessing large amounts of surface IgA was continuously passaged *in vitro* for 2 yr. During this period, fluorescence-activated cell sorter analysis indicated the development of subpopulations possessing decreased amounts of surface IgA. Cells from these variant subpopulations were isolated by first using the cell sorter to enrich for cells with decreased amounts of surface IgA and then cloning the selected population in soft agar. The 50 sublines that were isolated showed heritable differences in their levels of surface IgA and H-2 antigens and in their rates of myeloma protein secretion. Sublines having either large amounts, intermediate amounts, or an absence of surface IgA also had corresponding large amounts, intermediate amounts, or an absence of myeloma protein secretion. In contrast, a decrease or loss of surface immunoglobulin did not correlate with decrease or loss of viral envelope glycoprotein gp71 and H-2 antigens. The variants did not resemble the phenotypes of less-differentiated normal lymphocyte populations of the B-cell lineage. The isolation and characterization of these

variants allow the mechanisms and pathways of tumor cell differentiation to be studied along with the regulation and function of cell-surface proteins. (36 refs)

- 79-5265 Amino Acid Sequence of a Mouse Immunoglobulin μ Chain. (Eng) Kehry, M. (Div. Biology, California Inst. Technology, Pasadena, CA 91125); Sibley, C.; Fuhrman, J.; Schilling, J.; Hood, L. E. *Proc Natl Acad Sci USA* 76(6): 2932-2936; 1979.

The amino acid sequence of the secreted μ chain derived from the BALB/c mouse myeloma tumor MOPC 104E is reported. The $C\mu$ region contains four consecutive homology regions of approx 110 residues and a COOH-terminal region of 19 residues. A comparison of this μ chain with a complete μ chain sequence from human (Ou) and a partial μ chain sequence from dog (Moo) revealed a striking gradient of increasing homology from the NH_2 -terminal to the COOH-terminal portion of these μ chains, with the former being the least and the latter the most highly conserved. Four of the five sites of carbohydrate attachment appeared to be at identical residue positions when the constant regions of the mouse and human μ chains were compared. The μ chain of MOPC 104E has a carbohydrate moiety attached in the second hypervariable region. This is particularly interesting in view of the fact that MOPC 104E binds α -(1-3)-dextran, a simple carbohydrate. The structure of the secreted μ chain places several constraints on the membrane-bound μ chain of the IgM receptor molecule. (44 refs)

- 79-5266 Progressive Hypogammaglobulinaemia in a Child Born to a Mother with Hodgkin's Disease. (Eng) Evans, D. I. (Royal Manchester Children's Hosp., Pendlebury, Manchester M27 1HA, England); Burn, J. L. *Arch Dis Child* 54(4): 313-315; 1979.

A 29-yr-old woman developed Hodgkin's disease (nodular sclerosis) in the third trimester of pregnancy and gave birth to a boy who developed common variable immunodeficiency. Initially, the boy's IgG levels were normal, his IgA and IgM levels were low, and he had an antibody deficiency. IgG levels fell progressively over 4 yr. Cellular immunity was normal. It is suggested that this is a further family with immune deficiency presenting with common variable immunodeficiency and lymphoid malignancy. The father and an elder child were normal. (7 refs)

- 79-5267 Family Studies in Acute Leukemia in Childhood: A Possible Association with Autoimmune Disease. (Eng) Till, M. (Dept. Haematology, Inst. Child Health and Hosp. Sick Children, Great Ormond St., London WC1N 3JH, England); Rapson, N.; Smith, P. G. *Br J Cancer* 40(1): 62-71; 1979.

Medical histories of themselves and their first-degree relatives were obtained from the parents of 82 leukemic children [54 acute lymphoblastic (ALL), 28 acute myeloblastic (AML)] and from control couples matched for age. The possibility of primary familial immunological abnormality as an etiological factor in childhood leukemia was suggested by the fact that some infections were reported significantly more frequently by the parents than by the controls. This possibility was supported by the finding of a significantly ($P < 0.02$) increased prevalence of autoimmune disorders (eg, rheumatic fever and thyroid disorders associated with thyrotoxicosis or myxedema) among the ALL families, compared with the controls. No significant differences were found for other conditions such as peptic ulcer, infectious hepatitis, tuberculosis, or malignant disease. An analogy is drawn between these families and Down's syndrome and NZB mice, in which diminished T-cell function is associated with autoimmune disease and lymphoid neoplasia. Varicella and herpes zoster occurred, respectively, in 2 ALL mothers during their pregnancies involving the patients. This supports previous evidence that antenatal varicella infections may be an etiological factor in some cases of ALL. (17 refs)

- 79-5268 B-Cell Lymphoma Lacking Fc- and C3d-Receptors. (Eng) Thiel, E. (Abteilung Immunologie, Instituts für Hamatologie, GSF München, Landwehrstrasse 61, D-8000 Munich 2, W. Germany). *Blut* 37(6): 307-312; 1978.

Various cell-surface markers were studied in the lymphocytes from a 61-yr-old man with lymphosarcoma cell leukemia. Immunofluorescence and immunoradiography tests of the surface immunoglobulins (SIg) of the patient's lymphocytes revealed the monoclonal expression of IgM-type SIg of high density. This finding confirmed the B-cell origin of the leukemia. Interestingly, no Fc or C3d receptors could be demonstrated by various techniques. Only 22% of the leukemic cells expressed C3b receptors. The failure of the lymphocytes to form rosettes with mouse RBC was an additional surface feature that distinguished this disorder from ordinary B-cell type chronic lymphatic leukemia. The phenotype of the leukemia cells corresponded to that of less-differentiated B lymphocytes. (23 refs)

- 79-5269 Premature Multiple Bowen's Disease in Poikiloderma Congenitale with Warty Hyperkeratoses. (Eng) Haneke, E. (Dermatologische Universitätsklinik, Hartmannstrasse 14, D-8520 Erlangen, W. Germany); Gutschmidt, E. *Dermatologica* 158(5): 384-388; 1979.

A gradual malignant degeneration of verrucous hyperkeratoses was observed in a young girl with poikiloderma congenitale (PC) and cellular immune defi-

ciency. Although topical immunotherapy with dinitrochlorobenzene, initiated at age 14, resulted in the disappearance of numerous hyperkeratoses and in partial restoration of T-cell functions (eg, phytohemagglutinin lymphocyte stimulation index), the warty lesions recurred at age 15 and 16. Histological examination confirmed their transformation to highly malignant Bowen's lesions. The immune deficiency in this PC patient was also associated with impaired WBC function and reduction of B lymphocytes in the peripheral blood. (12 refs)

- 79-5270 A Serologically Detected Tumour-specific Membrane Antigen of Murine Lymphomas Which Is Not the Target for Syngeneic Graft Rejection. (Eng) Davey, G. C. (Div. Tumor Immunology, Chester Beatty Res. Inst., Belmont, Sutton, Surrey, England); Currie, G. A.; Alexander, P. *Br J Cancer* 40(1): 168-170; 1979.

Experiments demonstrating the presence, in the membrane of murine (DBA/2) lymphomas, of a tumor-specific cross-reacting antigen that does not act as a target for graft rejection are presented. Mice were injected ip with 10^7 previously irradiated (5,000 rads) lymphoma cells (SL/2, (L5178Y/E or L5178Y/ES) on day 0 and challenged ip with live cells on day 7 (10^3 to 10^5 cells). L5178Y/ES was less immunogenic than L5178Y/E, and there was no cross-protection between them; SL/2 was of intermediate immunogenicity and showed no cross-protection with L5178Y/E. An antiserum to SL/2 was raised in allogeneic mice with cells pretreated with anti-DBA/2 serum. The antiserum was initially toxic to both normal and malignant DBA/2 tissues, but after three absorptions on packed DBA/2 cells for 1-2 hr at 4 C, the antiserum had no toxicity for normal DBA/2 spleen cells, lymph node cells, or thymocytes or for two non-DBA/2 lymphomas, TLX-9 and TLC-5. However it was still highly cytotoxic in the presence of complement for SL/2, L5778Y/E, and L5178Y/ES. These data suggest that the antiserum recognizes a tumor-specific membrane component common to the three DBA/2 lymphomas. (6 refs)

- 79-5271 Heterotransplantation of Human Basal Cell Carcinomas in "Nude" Mice. (Eng) Pawlowski, A. (Clinical Science Div., Univ. Toronto, Medical Sciences Bldg., Room 7318, Toronto M4S 1A8, Canada); Haberman, H. F. *J Invest Dermatol* 72(6): 310-313; 1979.

The heterotransplantation of basal cell carcinomas (BCC's) from 10 human patients into 25 nude mice by grafting and sc inoculation was studied. BCC's developed in 2/12 mice given tumor grafts and in 3/13 mice inoculated sc. In the two mice with grafted tumors, typical islands of closely

packed tumor cells were visible in the dermis, whereas tumor cells in the animals with sc implants did not form these characteristic islands. Union between human and mouse epidermis was observed in two mice with grafted BCC's and in three other mice in which BCC's were not identified. Of the 20 mice in which the tumor did not take, complete necrosis of the implant was observed in 7, an inflammatory infiltrate appeared in the skin of 5, and increased skin vasculature and innervation was observed in 6. Seventy days after transplantation and 2 wk after the disappearance of the inoculum, one mouse developed a lymphoblastic/lymphocytic lymphoma. Immunological, vascular, stromal, and other environmental factors may have accounted for the low percentage of tumor takes. (17 refs)

- 79-5272 Vasculitis and Sjogren's Syndrome with IgA-IgG Cryoglobulinemia Terminating in Immunoblastic Sarcoma. (Eng) Aizawa, Y. (Dept. Internal Medicine, Keio Univ., 35 Shinanomachi, Shinjuku-Ku, Tokyo, Japan); Zawadzki, Z. A.; Micoloughi, T. S.; McDowell, J. W.; Neiman, R. S. *Am J Med* 67(1): 160-166; 1979.

Clinical, immunochemical, and pathologic findings in a 68-yr-old woman with a 12-yr history of systemic vasculitis and arthralgia who developed generalized lymphadenopathy and other manifestations of Sjogren's syndrome are reported. An unusual immunologic feature was hypogammaglobulinemia and IgA monoclonal immunoglobulinemia with mixed IgA-IgG cryoglobulin. At autopsy, the histopathologic findings were compatible with immunoblastic sarcoma. The monoclonal IgA protein, found in serum and the pleural and pericardial fluids, showed rheumatoid factor activity. Immunocytes from the immunoblastic sarcoma were found to be the source of the monoclonal IgA protein. (17 refs)

- 79-5273 Immunosuppression by a Mouse Tumor Resembles Antigenic Competition. (Eng) Cocito, C. G. (Dept. Microbiology and Genetics, Inst. Cell Pathology, Univ. Louvain, Medical Sch., Brussels, Belgium); Michot, B.; Radovich, J.; Talmage, D. W. *Proc Natl Acad Sci USA* 76(6): 2895-2897; 1979.

The ip injection of γ -irradiated, UV-irradiated or unirradiated P-185 tumor cells into syngeneic (DBA2) or allogeneic (C3H) mice suppressed the immune response to a subsequent ip injection of sheep RBC in a manner similar to the suppression caused by the injection of horse RBC and termed antigenic competition. In both cases, the greatest suppression occurred when the sheep RBC were injected at the same site (ip) as the tumor antigen and in a dose of 10^8 RBC or less. (10 refs)

- 79-5274 Suppression of Naturally Occurring Antitissue Antibodies During Growth and after Removal of Tumours. (Eng) Chandradasa, K. D. (Dept. Immunology, Univ. Liverpool, P.O. Box 147, Liverpool L69 3BX, England); Elson, C. J. *Gann* 70(3): 261-266; 1979.

The level and type of circulating antitumor antibodies were examined during tumor growth and during the induction of tumor immunity in inbred Wistar rats. The sera of normal rats were active in the complement fixation test against isogenic tumor homogenates. This activity was heat-labile, and it sedimented with IgM globulins upon zone ultracentrifugation in sucrose density gradients. Sera from rats bearing progressively growing tumors and sera from rats that had their tumors excised were less active than normal rat sera in the complement fixation test against isogenic tumor and liver homogenates. This suppression of naturally occurring antitissue antibodies may be a specific process related to the host immune response to the tumor. (33 refs)

- 79-5275 Low Natural-Killer-Cell Activity in Familial Melanoma Patients and their Relatives. (Eng) Hersey, P. (Kanematsu Memorial Inst., Medical Res. Dept., Sydney Hosp., Macquarie St., Sydney, New South Wales 2000, Australia); Edwards, A.; Honeyman, E. M.; McCarthy, W. H. *Br J Cancer* 40(1): 113-122; 1979.

Fifteen melanoma patients who had one or more close relatives with melanoma were studied for their natural killer cell (NK) activity against cultured melanoma cells and Chang cells. A high proportion of the patients and their relatives had low NK activity against these target cells. In most of the patients, this response could not be attributed to general depression of their immune function, since B- and T-cell numbers and the mitogenic response to phytohemagglutinin were within normal limits. The levels of NK activity of the patients and their relatives were found to be significantly correlated, suggesting that the NK activity in these families may have been genetically (or environmentally) determined. Several genetic markers were examined in the patients and their relatives for association with the disease state and NK activity. No association with histocompatibility (HLA) antigens or ABO blood groups were detected, but there was a low incidence of the Rhesus-negative phenotype in the patients (the Rh phenotype had previously been associated with high NK activity). The results indicate that NK activity has a familial association in families with a high incidence of melanoma, and they raise the question whether low NK activity may be one of the predisposing factors in the development of familial melanoma. (15 refs)

- 79-5276 AU Cell-Surface Antigen of Human Malignant Melanoma: Solubilization and Partial Characterization. (Eng) Carey, T. E. (Dept. Otorhinolaryngology, KHRI, Univ. Michigan Medical Center, Rm. 6020, 1301 E. Ann St., Ann Arbor, MI 48109); Lloyd, K. O.; Takahashi, T.; Travassos, L. R.; Old, L. J. *Proc Natl Acad Sci USA* 76(6): 2898-2902; 1979.

Antibody-inhibition tests were used to follow the solubilization and partial characterization of AU antigen, a unique tumor antigen restricted to the cell surface of melanoma cells from one patient (AU). The AU melanoma cell line is designated SK-MEL-28. Limited papain digestion (4-10 units/ml used with $5 \cdot 10^7$ cells/ml at 37 C for 30 min) was found to solubilize AU antigen along with B₂-microglobulin (B₂m) and histocompatibility locus antigen (HLA) allogeneic and xenogeneic specificities. Comparable papain treatment of other melanoma and nonmelanoma cell lines solubilized B₂m and HLA but not AU antigen. The max yield of AU antigen occurred after short (5-15 min) digestion times, whereas longer digestion times (up to 90 min) were required to maximize B₂m and HLA release. AU antigen was not immunoprecipitated by rabbit antiserum against B₂m or HLA under conditions leading to partial or complete removal of B₂m or HLA, showing that molecules with AU reactivity do not carry B₂m or HLA determinants. After affinity chromatography fractionation on a *Lens culinaris* hemagglutinin-agarose column, the specific activity of AU antigen was 30-50 times greater in the mannoside-eluted pooled fraction, indicating that molecules with AU determinants are glycoproteins, at least in part. When a papain digest of SK-MEL-28 cells was fractionated on a Sephadex G-150 column, about one-third of the AU activity eluted in the void volume of the column, and the major peak of AU activity eluted after the major protein peak in the mol wt range of 20,000-50,000 daltons. (13 refs)

- 79-5277 Psoriasis and Cancer (2 Letters to Editor). (Eng) Polani, P. E. (Pediatric Res. Unit, Guy's Hosp. Medical Sch., London SE1 9RT, England); Shuster, S.; Chapman, P. H.; Rawlins, M. D. *Br Med J* 1(6172): 1215; 1979.

The relation of psoriasis to histocompatibility antigen (HLA) haplotypes would be of interest in determining why, as determined in a previous study, psoriatics appear to be relatively resistant to cancer. Impaired aryl hydrocarbon hydroxylase (AHH) activity in psoriatic skin was also noted. The authors of the study reply that recent HLA analyses of psoriasis patients with decreased epidermal AHH activity showed that they had an increased frequency of BW17 antigens. (5 refs)

- 79-5278 Variations in the Level of Haematogenous Antitumor Immunity During Progressive Tumour Growth and Spontaneous Blood-borne Metastatic Spread. (Eng) Proctor, J. W. (Div. Radiation Oncology, Allegheny General Hosp., 320 E. North Ave., Pittsburgh, PA 15212); Mastromatteo, W. P.; Antos, M.; Hedderson, E. D. *Oncology* 36(2): 49-54; 1979.

Inbred DBA₂ mice bearing the syngeneic 1699 mammary tumor in their hind limb were challenged iv with ¹²⁵I-iododeoxyuridine-labeled single 1699 cell suspensions, and the amount of radioactivity in the lungs was compared 20-24 hr later with that in the lungs of normal mice or in those of mice bearing the antigenically unrelated syngeneic SaD₂ tumor. An immunologically specific decrease in radioactivity was evident at various times after tumor induction, depending on the number of cells used to induce the leg tumors, but the radioactivity fell below that in normal mice as the leg tumors progressed beyond a wt of approx 1 g. As assessed by microscopic scanning of serial histological sections of the same lungs, the incidence of spontaneous metastases rose to between 80% and 100% immediately after the amount of cell loss from the lungs of the tumor-bearing mice returned to that of the normal controls. This extremely rapid series of events does not allow a definitive conclusion as to whether immunity failed and led to metastatic spread or vice versa, but it does underline the strong association of immunity with the blood-borne dissemination of tumor cells in this tumor system. Following excision of the tumors, in no instance was immunity detected 14 days later, and, in a single experiment, it did not reach detectable limits until 25 days after excision, a time when the incidence of lung metastases fell to 14% as a result of spontaneous regression. (23 refs)

- 79-5279 Structure of Tumor Antigen on Hybrid Cells Between Mouse Mammary Ascites Tumor and Mouse Fibroblast L Cells. (Eng) Kubota, K. (The Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104). *Int J Cancer* 24(1): 114-120; 1979.

Somatic cell hybrids between mouse fibroblast L cells and MM2 mouse mammary ascites tumor cells grown in BALB/c mice were isolated, and the structures of the tumor-associated surface antigens (TASA's) of the hybrid cells and the parental cells were investigated by radioiodination of membrane proteins, immunoprecipitation with a specific antiserum against the TASA's of MM2 tumor (anti-MM2 serum), and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Two molecules of 105,000 daltons (105K) and 76K were detected on the MM2 cell surface, but no MM2 tumor antigen was detected on the mouse L cells. On the hybrids, molecules of 48K-51K and 12K were observed in addition to the two MM2 tumor antigens. On Sendai virus-infected mouse L cells, only a 68K molecule was detected by the anti-MM2 serum. This

molecule was also detected by normal mouse serum, which indicates that antibodies against Sendai virus were present in both the anti-MM2 and normal mouse sera used and that the molecules detected on the hybrid cells were distinguishable from possible viral components of Sendai virus on the hybrid cells. Thus, the somatic cell hybrids expressed on their surface the molecules that were not expressed on either parent cell. The newly detected molecules had an electrophoretic pattern that was similar to that of H-2 antigen. (20 refs)

- 79-5280 A New Experimental Model of Human Cachexia. (Eng) Strain, A. J. (Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England); Easty, G. C.; Neville, A. M. *Invest Cell Pathol* 2(2): 87-96; 1979.

A renal cell carcinoma removed from a man who had lost 30 kg in the 2 mo preceding surgery was grown as a nonmetastasizing transplantable xenograft in immune-suppressed female CBA/lac mice. The tumor produced a considerable wt loss (>25%) in the mice at a stage when it comprised <5% of the total body wt. A slight fall in food intake of the tumor-bearing mice was noted, but animals bearing other noncachectic mouse and human tumors had much lower food intakes without accompanying wt loss. No obvious defects in gastrointestinal absorption were detected, nor was any gross increase in the basal metabolic rate observed. The precise mechanism producing the severe cachexia remains to be established, but elaboration of humoral factors by the tumor seems probable. This model of cachexia bears a closer relation to the clinical situation than do other experimental animal tumor models currently available. (27 refs)

- 79-5281 Multiple Primary Tumors in Patients with Urological Tumors: Reduced Immunocompetence? (Ger) Klippel, K. F. (Urologische Klinik, Johannes-Gutenberg-Universität, Langenbeckstrasse 1, D-6500 Mainz, W. Germany); Hutschenreiter, G.; Jacobi, G.; Graff, J. *Onkologie* 2(1): 12-16; 1979.

The immune status of 55 patients with multiple primary malignant tumors, including at least one urological tumor, and of control patients with solitary tumors was studied by determining immunoglobulin levels, B- and T-cell counts, and the response of lymphocytes to stimulation and by the dinitrochlorobenzene skin test. The average age of the 55 patients was 58.1 yr at the manifestation of the first tumor and 64.3 yr at the manifestation of the second tumor. The male:female ratio was 4:1. The first tumors included hypernephromas, carcinomas of the bladder, prostate,

IMMUNOLOGY

penis, testicles, colon, uterine cervix, vagina, lungs, larynx, pharynx, salivary glands, ovaries, and tongue, and myeloproliferative neoplasms. The second tumors included carcinomas of the prostate, lungs, anus, uterus, urinary bladder, colon, urethra, and renal pelvis; hypernephromas; malignant teratomas; hepatocellular carcinomas; rhabdomyosarcomas; and seminomas. The immunological tests failed to show any significant differences in immune status between the patients with double tumors and the control patients with solitary tumors, but they revealed that both groups had a diminished immunocompetence compared with another control group of patients with nonmalignant diseases. (15 refs)

See also:

- *(Rev.): 79-4842, 79-4873, 79-4874, 79-4875, 79-4877,
79-4890, 79-4895, 79-4896, 79-4899, 79-4900,
79-4901, 79-4902, 79-4903, 79-4904, 79-4905,
79-4906, 79-4907, 79-4911.
- *(Chem.): 79-4992, 79-4994, 79-5016, 79-5033, 79-5045,
79-5053, 79-5054.
- *(Viral): 79-5121, 79-5122, 79-5123, 79-5125, 79-5126,
79-5152, 79-5158, 79-5159, 79-5163, 79-5164,
79-5165, 79-5166, 79-5167, 79-5170, 79-5172,
79-5173, 79-5181, 79-5182, 79-5184, 79-5191,
79-5192, 79-5194, 79-5217.
- *(Path.): 79-5286, 79-5290, 79-5294, 79-5295, 79-5331.

PATHOGENESIS

- 79-5282 Cell Interactions in the Differentiation of a Melanotic Tumor in *Drosophila*. (Eng) Rizki, R. M. (Div. Biological Sciences, Univ. Michigan, Ann Arbor, MI 48109); Rizki, T. M. *Differentiation* 12(3): 167-178; 1979.

The cellular events in the formation of melanotic tumors in the tumor-W (*tu-W*) mutant larva of *Drosophila melanogaster* were studied. The first step was transition of spherical plasmocytes into flattened, disk-like variants called lamellocytes. This morphologic transition was accompanied by extrusion of intracellular fluids. Melanotic tumor formation was limited to the caudal region of the larval fat body. Globular and membranous materials appeared at the intercellular boundaries of the adipose cells, and the hemocytes actively engulfed materials oozing from the surfaces of these cells. The basement membrane of the caudal fat body underwent dissolution and lamellocytes and hemocytes in transition to the lamellocytic form landed on the adipose cell surfaces which lacked basement membrane. Layering of hemocyte upon hemocyte continued until a laminated capsular wall surrounded the entire area of adipose cells. Regions between apposing lamellocytes were traversed by electron dense fibrillary material which extended into the cytoplasm of adjacent cells. Small vesicles originating from the surfaces of the hemocytes were observed. They tended to adhere to the hemocyte surface and were trapped between the lamellocytes. It is suggested that the vesicles play a role in lamellocyte-to-lamellocyte adhesion during the initial stages of hemocyte aggregation at the tumor site. (15 refs)

- 79-5283 Genetic Associations of Transitional Cell Carcinoma. (Eng) Herring, D. W. (Dept. Surgery, Dryburn Hosp., Durham, England); Cartwright, R. A.; Williams, D. D. *Br J Urol* 51(2): 73-77; 1979.

A series of 101 cases of transitional cell carcinoma (TCC) was contrasted with a control series for several genetic parameters. The three genetic associations demonstrated in the TCC patients were ABO A, HLA B5 and HLA CW4 gene frequencies higher than expected. Classification of the natural history of the disease showed that HLA frequencies vary with the severity of the disease. (16 refs)

- 79-5284 Autopsy Case of Histiocytic Medullary Reticulosis in an Infant. (Jpn) Oku, T. (Se-

cond Dept. Pathology, Yamaguchi Univ. Sch. Medicine, Ube, Yamaguchi Prefecture 755, Japan); Sasai, K.; Ogino, T.; Tani, S.; Takahashi, M. *Gan No Rinsho* 25(6): 644-647; 1979.

A 20-mo-old boy presented with hepatosplenomegaly, anemia, and a tendency to hemorrhage. Peripheral blood levels of erythroblasts and monocytes were suggestive of erythroleukemia or monocytic leukemia; Letterer-Siwe disease was also considered because of the many atypical histiocytes in the bone marrow. The child died 23 days after admission due to severe intestinal bleeding. A diagnosis of histiocytic medullary reticulosis was established on the basis of autopsy findings. The bleeding was ascribed to histiocytic infiltration of the intestinal mucosa. (25 refs)

- 79-5285 Invasion of Malignant C3H Mouse Fibroblasts from Aggregates Transplanted into the Auricles of Syngenic Mice. (Eng) Meyvisch, C. (Dept. Experimental Cancerology, Clinic for Radiotherapy and Nuclear Medicine, Academic Hosp., De Pintelaan 135, B 9000 Ghent, Belgium); Mareel, M. *Virchows Arch [Cell Pathol]* 30(1): 113-122; 1979.

Spheroid aggregates of malignant fibroblasts (MO₄ cells), which are invasive in vitro and in vivo, were implanted sc into the auricles of syngeneic female inbred C3H/HeA mice to study early stages of invasion. Animals were killed 6 hr-30 days after inoculation, and the auricles were studied in serial sections. After 6 hr, a few MO₄ cells showed cytoplasmic extensions in contact with connective tissue or with muscle cells. Polymorphonuclear WBC (PMN's), mainly neutrophils, (PMN's) were present in the outer part of the MO₄ aggregate. After 24 hr, the MO₄ aggregates contained macrophages and lymphocytes as well as PMN's. Many MO₄ cells at the periphery of the aggregate had assumed a stretched configuration. After 2 days, MO₄ cells were further away from the aggregate, suggesting progressive invasion. Newly formed blood vessels were observed in the vicinity of the aggregate. In most auricles fixed after 4 days, no MO₄ cells were found at the site of the original aggregate. Proliferative foci in auricles inoculated with an MO₄-aggregate differed from control auricles in their higher cell density and their lower collagen content. Palpable tumors were present after 20-30 days; they showed the histological characteristics of fibrosarcomas. It is concluded that a small number of invasive MO₄ cells will grow into a palpable tumor at a site where there is a favorable microenvironment. (26 refs)

- 79-5286 Expression of Malignancy in Hybrids Between Normal and Malignant Cells. (Eng) Croce, C. M. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Barrick, J.; Linnenbach, A.; Koprowski, H. *J Cell Physiol* 99(3): 279-286; 1979.

Somatic cell hybrids between normal human fibroblasts, phenotypically normal mouse fibroblasts, or mouse peritoneal macrophages and HT1080 human diploid fibrosarcoma cells were studied for their ability to form tumors in BALB/c nude mice. Hybrids between normal and malignant human cells were tumorigenic, and there was no consistent pattern of reduction or increase in the number of chromosomes or any specific human chromosome pair. Nontumorigenic hybrids between D98 hypoxanthine phosphoribosyltransferase-deficient human carcinoma cells and normal human diploid fibroblasts were fused with cells from a patient with β -glucuronidase deficiency. Only 1/4 of the hybrid lines was tumorigenic in nude mice; the tumors were positive for glucose-6-phosphate dehydrogenase types A and B. Hybrids between phenotypically normal mouse cells and HT1080 cells were tumorigenic, indicating that the normal mouse genome is incapable of suppressing malignancy. Hybrids between HT1080 cells and mouse peritoneal macrophages were also tumorigenic, indicating that the presence of mouse chromosome 4 does not result in the suppression of malignancy. The data indicate that tumorigenic behavior is expressed as a dominant trait in both human-human and mouse-human hybrid cells. (21 refs)

- 79-5287 Inflammatory Oncotaxis (Letter to Editor). (Eng) DerHagopian, R. P. (Univ. Miami Sch. Medicine, Miami, FL). *JAMA* 241(21): 2264; 1979.

The possibility of the occurrence of malignant tumors in old sites of inflammation such as scars is discussed. The capillaries in these loci have been shown to end blindly. These dead-end capillaries may act as easy entrapment points for circulating malignant cells. (2 refs)

- 79-5288 Macrocytic Anemia, Thrombocytosis and Nonlobulated Megakaryocytes. The 5q-Syndrome, a Distinct Entity. (Eng) Mahmood, T. (Denver Veterans Admin. Medical Center, 1055 Clermont St., Denver, CO 80220); Robinson, W. A.; Hamstra, R. D.; Wallner, S. F. *Am J Med* 66(6): 946-950; 1979.

The clinical, hematologic, and histologic characteristics of six patients (5 women, 1 man, aged 42-79 yr) with refractory anemia showing deletion of the long arm of chromosome 5 are described. These patients had a distinct hematologic picture: macrocytic anemia of mild to moderate severity, a normal to low WBC count, and an increased platelet count. The long arm of chromosome 5 was

deleted in most of the bone marrow metaphases. The main cause of anemia was underproduction with decreased erythroid precursors in the bone marrow and no increase in peripheral blood reticulocytes. Two of five patients responded transiently to the administration of androgens. The bone marrow growth pattern in semisolid agar was evaluated for three patients, and it was found to be normal and distinct from that of patients with preleukemia. In a follow-up of up to 5 yr, no patient had changed hematologically and in none had leukemia developed. The 5q syndrome is a distinct hematologic entity and is probably more common than previously realized. This diagnosis may have prognostic implications. (20 refs)

- 79-5289 Acute Leukemia and Preleukemia in Eight Males in a Family: An X-linked Disorder? (Eng) Li, F. P. (44 Binney St., Boston, MA 02115); Marchetto, D. J.; Vawter, G. F. *Am J Hematol* 6(1): 61-69; 1979.

The occurrence of acute leukemia or potentially preleukemic conditions in eight male members of a French-Canadian family is reported. The affected members were descendants of a single man: two grandsons and a great-grandson resulting from his first marriage; and two sons, two grandsons, and a great-grandson resulting from his second marriage. In seven patients, the underlying clinical disorder appeared to be acute leukemia that followed a period of pancytopenia. Aplastic anemia was initially diagnosed in 3/7, and three additional patients had histories of bone marrow hypoplasia and peripheral cytopenias; the seventh patient had typical acute lymphocytic leukemia. Light-chain disease in the eighth patient was distinct from preleukemia, but it is another hematologic disease in which acute leukemia tends to develop. An X-linked inheritance of the fatal hematologic disorders was suggested, although this mechanism required that the two wives of the proband be carriers of the same rare disease. (27 refs)

- 79-5290 Familial Lymphoproliferative Malignancy: Clinical and Laboratory Follow-up. (Eng) Blattner, W. A. (NCI, NIH, Bethesda, MD 20014); Dean, J. H.; Fraumeni, J. F. *Ann Intern Med* 90(6): 943-944; 1979.

The occurrence of B-cell neoplasms and immune defects among descendants and surviving first-degree relatives of three siblings (2 brothers, cases 11-1 and 11-6, and a sister, case 11-10) with chronic lymphocytic leukemia (CLL) is reported. The daughter of 11-6 developed a poorly differentiated lymphocytic lymphoma, another brother developed a squamous cell carcinoma of the lung, and a granddaughter of 11-6 developed a well-differentiated squamous cell carcinoma in her thigh. Persistent immune defects in

several members of this family link the predisposition to B-cell neoplasms to an inherited defect in immune regulation. The immune defects took various forms, usually impaired responses to phytohemagglutinin, immunoglobulin abnormalities, and depressed stimulation in mixed WBC culture. No clear relationship was found between the HLA haplotype of II-6 (HLA-A2, B15, CW3, and DW1) and the immune dysfunction in the family. However, because this haplotype was shared by the family members with a lymphoproliferative malignancy, susceptibility may be related to a major histocompatibility-associated gene. (10 refs)

- 79-5291 **The Preleukemic Syndrome. Correlation of In Vitro Parameters of Granulopoiesis with Clinical Features.** (Eng) Greenberg, P. L. (Veterans Admin. Hosp., 3801 Miranda Ave., Palo Alto, CA 94304); Mara, B. *Am J Med* 66(6): 951-958; 1979.

To determine the clinical utility of in vitro marrow culture techniques for evaluating the preleukemic syndrome, in vitro parameters of granulopoiesis were correlated with the clinical courses of 43 prospectively studied patients with the syndrome. The clinical features of these cytopenic patients with a marrow morphology showing hemopoietic dysplasia included the following: median age, 61 yr; combined cytopenias, 60%; low WBC alkaline phosphatase, 67%; splenomegaly, 33%; median survival, 18.9 mo; and 2-yr actuarial probability of survival, 55%. Transformation into acute myeloid leukemia occurred in 19 patients within a median period of 19.1 mo. Presenting pancytopenia was the only clinical feature indicative of subsequent acute transformation, with 69% of the patients undergoing such an evolution within a median period of 15 mo. Lethal infections were frequent during the preleukemic period. Abnormalities of in vitro marrow myeloid clonal growth were initially present in 72% of the patients showing significantly low granulocyte-monocyte colony-forming cell (CFU-GM) values and a high proportion of light-density CFU-GM. Persisting or progressive decrements in CFU-GM values sequentially occurred prior to or concomitant with acute transformation in six patients. Markedly diminished initial CFU-GM values (≤ 2 colonies/ 10^5 marrow cells) were predictive for a significantly decreased (19%) 2-yr probability of survival ($p < 0.004$), whereas no clinical feature showed this association. Marrow cell and urinary colony-stimulating activity output were normal during the chronic phase of the disorder. These in vitro myeloid culture studies are useful adjuncts to marrow morphology and clinical features for diagnostic and prognostic characterization of patients with this syndrome. (29 refs)

- 79-5292 **Contribution of Cytogenetics to the Study of Hemopathies.** (Fre) Cadotte, M. (Service de Cytogenetique, Hotel-Dieu de Montreal, Montreal, Canada). *Union Med Can* 108(5): 511-514; 1979.

The value of cytogenetic studies in the diagnosis of hemopathies is illustrated in two cases. In one case, detection of the Philadelphia chromosome permitted the diagnosis of leukemic infiltration vs a diagnosis of lymphoma. In a patient with polycythemia vera, leukemia was diagnosed after detection of the Philadelphia chromosome. (4 refs)

- 79-5293 **Subacute Myeloid Leukemia. A Clinical Review.** (Eng) Cohen, J. R. (Suite 202, 2410 Samaritan Drive, San Jose, CA 95124); Creger, W. P.; Greenberg, P. L.; Schrier, S. L. *Am J Med* 66(6): 959-966; 1979.

Data on 31 patients (22 men and 9 women aged 17-86 yr) who fit into the clinical spectrum of subacute myeloid leukemia were reviewed. Most patients were men with a median age of 61 yr. The interval from onset of symptoms to actual diagnosis was extremely variable, with a mean of 16 mo and a median of 6 mo. Most patients presented with anemia and thrombocytopenia, although the WBC count varied from striking leukopenia to marked leukocytosis. Examination of the bone marrow invariably revealed abnormalities of all cell lines with megaloblastoid erythropoiesis and dysplastic megakaryocytopoiesis. Although the white cell line showed a prominence of immature forms, there was more maturation than is seen in acute myeloid leukemia. Survival from diagnosis was variable, from < 1 mo to > 68 mo, with a median of only 6 mo. Anemia and hepatosplenomegaly were prognosticators of a poor outlook; patients with hepatosplenomegaly in association with either leukocytosis or thrombocytopenia had a particularly poor outlook, with a median survival of only 1.5 mo. Approx half the patients received chemotherapy with no demonstrated effect on survival. (27 refs)

- 79-5294 **Pathophysiology of Lymphocyte Transformation. A Study of So-called Composite Lymphomas.** (Eng) van den Tweel, J. G. (Dept. Pathology, Hematopathology Section, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Lukes, R. J.; Taylor, C. R. *Am J Clin Pathol* 71(5): 509-520; 1979.

The occurrence of two different histologic types of lymphoma in one organ, in two different organs at the same time, or during the course of the disease is an intriguing biologic phenomenon. An immunohistologic study was made of 10 such cases, 7 consisting of two different non-Hodgkin's lymphomas (NHL's) and 3 in which Hodgkin's disease (HD) was one of the components. The findings in the NHL group are in keeping with emerging immunologic and physiologic concepts; ie, the different component parts appear to represent different maturation stages of the

neoplastic B lymphocyte. In the cases in which HD and a NHL were observed, there was a surprising similarity between the malignant cells of both tumors when they were studied by immunoperoxidase techniques for anti-light-chain and anti-heavy-chain antibodies. These observations may serve to resurrect an old belief in the common origin of certain of the NHL's and, possibly, of HD. It is concluded that true composite lymphomas are extremely rare and that most of the cases described as such in the literature are, in reality, different morphologic expressions of a single malignant cell type, the lymphocyte. (33 refs)

- 79-5295 HLA Antigens in Familial Hodgkin's Disease. (Eng) Greene, M. H. (Environmental Epidemiology Branch, NCI, Landow Building, Room 3C-07, Bethesda, MD 20205); McKeen, E. A.; Li, F. P.; Blattner, W. A.; Fraumeni, J. F. *Int J Cancer* 23(6): 777-780; 1979.

The histocompatibility locus (HLA) antigen distribution in 19 men and 12 women with Hodgkin's disease from 13 multiple case families was studied. Of the 13 probands (so designated before testing), 7 had the Bw35 antigen; less than 2 were expected on the basis of the frequency of this antigen in the general population ($p = 0.01$). This antigen was present in 14/23 patients evaluated, all of the positive patients being between 15 and 44 yr old (median, 23 yr). There was no association between Bw35 and histologic subtype. In three families, Aw24 was linked with Bw35, and all but one patient in these families shared the haplotype 24-35. All three patients in one of these three families also carried the Cw4 antigen. Antigen Bw37 also occurred more frequently than expected in the 31 patients (3 observed, 0.5 expected, $p = 0.03$). No significant antigen deficits were observed. These results suggest that immunogenetic mechanisms account at least in part for the familial predisposition to Hodgkin's disease. (28 refs)

- 79-5296 Differential Counts of Neutrophil, Eosinophil, and Macrophage Colonies in Cultures from Human Bone Marrow and Peripheral Blood. (Eng) Nissen-Druey, C. (Abteilung Hamatologie, Medizinische Universitätsklinik, Kantonsspital Basel, Petersgraben 8, CH-4000 Basel, Switzerland); Speck, B. *Blut* 37(5): 241-248; 1978.

Neutrophil, eosinophil, and macrophage colonies were counted in cultures of bone marrow and peripheral blood from 246 patients with a variety of diseases and 80 normal controls. Eosinophil and macrophage colonies were increased in patients with carcinomas, Hodgkin's disease, lymphoma with bone marrow involvement, graft-vs-host disease, myeloma, and acute myelogenous leukemia in remission. They were virtually absent in cultures from the peripheral blood of patients with chronic granulocytic

leukemia and myelofibrosis, and they were reduced in patients with nonmalignant leukopenias. Normal peripheral blood cultures had a higher proportion of eosinophil colonies than normal bone marrow cultures but a lower proportion of macrophage colonies. It is concluded that in vitro conditions favor eosinophil commitment. As a nonspecific sign of disease, increased commitment is therefore more likely to be recognized in vitro than in vivo. (5 refs)

- 79-5297 Histiocytic Lymphoma in a Patient with Lennert's Lymphoma: Report of a Case with Unusual Cytoplasmic Inclusions. (Eng) Miller, R. (Dept. Pathology, Medical Univ. South Carolina, 171 Ashley Ave., Charleston, SC 29403); Spicer, S. S.; Kurtz, S. M. *Arch Pathol Lab Med* 103(6): 279-283; 1979.

A case of Lennert's lymphoma followed by histiocytic lymphoma is presented. The patient, a 55-yr-old woman who presented with lower left quadrant abdominal pain, wt loss, and a palpable mass in the epigastric region, also suffered from Lennert's lymphoma diagnosed 3 yr earlier. Exploratory laparotomy revealed grossly enlarged lymph nodes in the mesenteric and para-aortic regions. The pathologic diagnosis was diffuse histiocytic lymphoma. Electron microscope examination demonstrated that many of the histiocytic lymphoma cells possessed a well-demarcated paranuclear accumulation of fine filaments. The filamentous inclusions contained free ribonucleoprotein particles and coated vesicles interspersed between the filaments. The inclusions stained strongly for IgG and less strongly for K and γ light chains. Immunostaining for IgA showed occasional cells with diffuse and paranuclear globular staining. No IgM was detected. The positive polyclonal staining of the paranuclear inclusions suggested aberrant immunoprotein production and indicated that the neoplasm was of B cell origin. (29 refs)

- 79-5298 Infiltrating Pituitary Neoplasms in the Rat. (Eng) Magnusson, G. (Dept. Pathology, Huntingdon Res. Centre, Huntingdon, PE18 6ES, England); Majeed, S. K.; Gopinath, C. *Lab Anim* 13(2): 111-113; 1979.

Spontaneous pituitary neoplasms occurred in 442/1,371 male and 596/1,238 female CFY Sprague-Dawley outbred specific-pathogen-free rats. In all but two males and nine females, the neoplasms were diagnosed as pituitary adenomas arising from the anterior lobe. In the other 11 rats, the pituitary tumors infiltrated the adjacent brain tissue. (9 refs)

- 79-5299 Medullary Carcinoma of the Thyroid: A Clinicopathologic and Ultrastructural Study in

a Patient with Sipple's Syndrome. (Eng) Clark, M. A. (Dept. Lab. Medicine, Div. Anatomic Pathology, Natl. Naval Medical Center, Bethesda, MD 20014); Lack, E. E.; Kramer, S. N. *Milit Med* 144(6): 381-384; 1979.

A case of Sipple's syndrome associated with medullary carcinoma of the thyroid (MCT) occurred in a 34-yr-old woman. Chemical evidence of hyperparathyroidism was detected prior to confirmation of elevated calcitonin levels. Ultrastructural studies of the MCT showed that there were two predominant cellular elements corresponding to light and dark cells, plus some intermediate forms. (12 refs)

79-5300 Incidental Medullary Thyroid Carcinoma in Sporadic Hyperparathyroidism. An Expansion of the Concept of C-Cell Hyperplasia. (Eng) LiVolsi, V. A. (Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar St., New Haven, CT 06510); Feind, C. R. *Am J Clin Pathol* 71(5): 595-599; 1979.

A 54-yr-old man and a 66-yr-old woman with sporadic primary hyperparathyroidism were found to harbor tiny medullary thyroid carcinomas. In addition, parafollicular cell hyperplasia was recognized in one of these thyroids by the use of an immunoperoxidase stain to localize calcitonin. Animal experiments support the theory that the hypercalcemia of parathyroid hormone excess evokes a calcitonin response from the parafollicular cells. The two patients appear to represent an extension of the concept of the progression of sporadic C-cell hyperplasia to neoplasia. It is concluded that the lesions in both had progressed to carcinoma, one of which metastasized. It is not believed that resolution of the hypercalcemic state by removal of the parathyroid adenoma could have reversed the neoplastic C-cell lesions. These two cases draw attention to the possible coexistence of true medullary thyroid cancer in patients with sporadic hyperparathyroidism. (27 refs)

79-5301 On the Natural History of Plummer's Disease. (Eng) Wiener, J. D. (Dept. Medicine, Academisch Ziekenhuis der VU, 1007 MB Amsterdam, Netherlands); de Vries, A. A. *Clin Nucl Med* 4(5): 181-190; 1979.

A series of 58 untreated patients with Plummer's disease (autonomous goiter) were re-examined on one or more occasions over periods of 1-12 yr. Gross clinical or scintigraphic changes were seen in 13 patients, minor changes in 14. However, the disease progressed rapidly in 2/300 other patients. Since low-grade malignancy has been reported in over 10% of the reported American cases of Plummer's disease, there may be more than a chance relationship between the two pathologies. In the absence of suspected thyrotoxic crises or malignancy, it is concluded that Plummer's disease may be left untreated. (31 refs)

79-5302 An Unusual Cause of Obstructive Jaundice. (Dut) Simonis, R. F. (Afdeling Inwendige Geneeskunde, Ziekenhuis Leyenburg, Leyweg 275, Hague, Netherlands); Smits, P. J.; Bender, J. *Tijdschr Gastroenterol* 21(3): 167-174; 1978.

A 69-yr-old man developed obstructive jaundice suggestive of pancreatic malignancy. A tumor found in the head of the pancreas proved to be a late metastasis of a renal cell carcinoma that had been removed by left nephrectomy 9 yr earlier. (15 refs)

79-5303 Severe Pancreatic Involvement in Three Generations in von Hippel-Lindau Disease. (Eng) Fishman, R. S. (Div. Gastroenterology and Internal Medicine, Mayo Clinic, Rochester, MN); Bartholomew, L. G. *Mayo Clin Proc* 54(5): 329-331; 1979.

Extensive pancreatic involvement in three patients with Von Hippel-Lindau disease (VHLD) is reported. The first patient was a 60-yr-old man who had at least six family members with tumors typical of VHLD. The other patients were the 20-yr-old daughter of this man and his mother, who was seen at age 39 yr. The first patient had a history of cerebellar hemangioendothelioma and a retinal angioma, an angiographically documented slow-growing vascular tumor involving the entire pancreas and many other abdominal organs, recent onset of insulin-dependent diabetes, and pronounced steatorrhea that responded to pancreatic extract. It was concluded that the abdominal tumor was part of the VHLD and that complete infiltration of the pancreas had led to exocrine and probably endocrine pancreatic insufficiency. There was no clinical or laboratory evidence to suggest small bowel or hepatic dysfunction. The other two patients had complete replacement of the pancreas by cysts but no overt pancreatic insufficiency. As of 1972, only 101 cases of visceral involvement in VHLD had been reported; the pancreas was affected in 24%. Benign cysts are the most common pancreatic lesions. (7 refs)

79-5304 Establishment and Characterization of a Human Neuroblastoma Cell Line in Tissue Culture. (Eng) Sekiguchi, M. (Dept. Clinical Oncology, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan); Oota, T.; Sakakibara, K.; Inui, N.; Fujii, G. *Jpn J Exp Med* 49(1): 67-83; 1979.

The characteristics of a new continuous human neuroblastoma line, GOTO, are described. The line was obtained from a tumor arising in the adrenal gland of a 13-mo-old male infant, and it has been maintained in tissue culture for 5 yr. The cells are small and fibroblastlike, and they grow in a dense layer. The population doubling time is approx 48 hr, and the modal chromosome number is near-

diploid. Neither marker chromosomes nor double minute chromosomes have been observed. Injection of 10^7 cells produced tumors in antithymocyte serum-treated hamsters and athymic nude mice, and the histological appearance of the tumors was consistent with that of an undifferentiated neuroblastoma. The neural features of the cells were also confirmed by ultrastructural examination. Biochemical analysis showed that this cell line is cholinergic. Morphological differentiation leading to neurite formation was induced by cultivation of the cells in serum-free medium. (50 refs)

- 79-5305 Peutz-Jeghers Syndrome. (Fre) Baillot, R. (Departement de Chirurgie, Hopital Maisonneuve-Rosemont, Montreal, PQ, Canada); Le Gresley, L. P.; Girard, R. M. *Can J Surg* 22(3): 207-211; 1979.

Peutz-Jeghers syndrome was diagnosed in a 17-yr-old boy and in a 21-yr-old woman. A recurrence of the polyps was seen in the boy 3 yr after polypectomy. An aunt and cousin of the woman with Peutz-Jeghers syndrome had mucocutaneous pigmentation, as did her child born 8 yr after she underwent surgery to remove esophageal polyps. (30 refs)

- 79-5306 Genetic Linkage Studies Between Congenital Adrenal Hyperplasia and the HLA Blood Group System. (Eng) Grosse-Wilde, H. (Institut für Med. Virologie und Immunologie, Universitätsklinikum Essen, Hufelandstrasse 55, D-4300 Essen 1, W. Germany); Weil, J.; Albert, E.; Scholz, S.; Bidlingmaier, F.; Sippel, W. G.; Knorr, D. *Immunogenetics* 8(1): 41-49; 1979.

The linkage between the histocompatibility (*HLA*) and the *C-21-hydroxylase* deficiency genes and its correlation with the results of a biochemical test for congenital adrenal hyperplasia (CAH) were studied. Seventeen families with one or two children suffering from CAH were not only typed for their *HLA-A*, *B*, and *D* antigens but also tested biochemically for CAH heterozygosity after ACTH stimulation. There was a close genetic linkage between CAH and *HLA*, indicating that the *C-21-hydroxylase* deficiency gene(s) causing CAH in the homozygous deficient state is located close to the *HLA* complex on chromosome 6, with an estimated recombination fraction of 0%-5%. *HLA* typing in 21 unrelated CAH patients revealed a statistically significant association with *HLA-B5* antigen, for a relative risk value of 5.8. There was a significant correlation ($p = 0.0025$) between the *HLA* segregation data and the CAH heterozygosity test results in relatives of CAH patients, although a few false-negative results in the CAH heterozygosity test were observed. Thus, the combination of *HLA* typing and this biochemical test currently

provides the most precise approach for detecting CAH carriers in families of CAH patients. (15 refs)

- 79-5307 Tumor Interaction with the Fibrinolytic System. (Eng) Malone, J. M. (Dept. Surgery, Arizona Health Sciences Center, Tucson, AZ 85724); Gervin, A. S.; Moore, W. S.; Keown, K. *J Surg Res* 26(5): 581-589; 1979.

Tumor interaction with the fibrinolytic system was evaluated, and the potential of tumor activation and inhibition of fibrinolysis as biologic markers for metastatic disease was studied. Normal tissue and tumor specimens were obtained from human patients. Most normal tissue demonstrated moderate amounts of fibrinolytic activity (200-600 mm^2), but no normal tissue other than liver demonstrated inhibition of fibrinolysis. All benign lesions showed significant activation of fibrinolysis but no inhibition of fibrinolysis. All malignant neoplasms, except two superficial spreading melanomas, demonstrated inhibition of fibrinolysis (33-312 mm^2). With the exception of embryonal cell carcinoma, all malignant neoplasms also demonstrated activation of fibrinolysis (12-1508 mm^2). Most malignant lesions without metastatic spread had fibrinolytic activity levels $<600 \text{ mm}^2$, whereas most tumors with metastatic spread had fibrinolytic activity levels $>600 \text{ mm}^2$. Nonmetastatic tumors had an av tumor activation/inhibition (A/I) ratio of 4.09; metastatic tumors had an av A/I ratio of 18.36. (32 refs)

- 79-5308 Familial Pheochromocytoma: A Report of 2 Cases in a Kindred. (Eng) Kaufman, J. J. (Dept. Surgery, Div. Urology, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA); Franklin, S. *J Urol* 121(6): 801-804; 1979.

The sixth and seventh documented cases of pheochromocytoma in one family are reported. The proband, a 36-yr-old woman, had classical features of adrenal medullary hyperfunction in addition to Raynaud's phenomenon. After surgical removal of the right adrenal gland, which contained a pheochromocytoma and a small paraganglioma, the patient was free of symptoms. The 12-yr-old son of the proband was discovered to have relatively asymptomatic sustained hypertension on routine examination. Biochemical and radiological tests confirmed the diagnosis of a left adrenal pheochromocytoma. (14 refs)

- 79-5309 Hormone-mediated Watery Diarrhea in a Family with Multiple Endocrine Neoplasms. (Eng) Hutcheon, D. F. (Johns Hopkins Hosp., Baltimore, MD 21212); Bayless, T. M.; Cameron, J. L.; Baylin, S. B. *Ann Intern Med* 90(6): 932-934; 1979.

The case reports of a father (age 63) and son (age 30) with pancreatic islet cell tumors and long histories of severe watery diarrhea (7 and 4 yr duration, respectively) are presented. The son had a pancreatic islet cell tumor associated with the pancreatic cholera syndrome and a parathyroid adenoma. The father had multiple islet cell adenomas and the Zollinger-Ellison syndrome. Pancreatic tumor tissue from each patient contained detectable gastrin and vasoactive intestinal peptide; however, a much higher gastrin concentration was found in the tumor tissue from the father and a much higher vasoactive intestinal peptide content was found in the tumor tissue from the son. Thus, watery diarrhea may be mediated by different hormones in families having multiple endocrine neoplasia. The precise cause of the diarrheal syndrome should be defined to ensure the proper therapy. (14 refs)

- 79-5310 Intracranial Tumors with Psychiatric Symptoms. Report of Three Cases. (Dan) Schmidt, J. (Afdeling B, Psykiatrisk ved Aarhus, Baekkelundsvej 14, DK-8240 Risskov, Denmark). *Ugeskr Laeger* 141(20): 1330-1331; 1979.

Brain tumors were found in three men, aged 62, 47, and 45 yr, undergoing treatment in a psychiatric ward; the initial diagnosis was alcoholic dementia, reactive psychosis, and endogenous depression, respectively. The tumors were identified as a meningioma of the olfactory nerve, a malignant tumor of the left frontoparietal lobe, and a meningeal sarcoma of the left frontotemporal region. Periodical disturbances of consciousness were typical symptoms. (8 refs)

- 79-5311 Primary Intracranial Epidermoid Carcinoma. Case Report. (Eng) Nosaka, Y. (Dept. Neurosurgery, Okayama Univ. Medical Sch., 2-5-1 Shikata-cho, Okayama, Japan); Nagao, S.; Tabuchi, K.; Nishimoto, A. *J Neurosurg* 50(6): 830-833; 1979.

The case report of a 46-yr-old man with a primary intracranial epidermoid carcinoma that was detected by computerized tomography (CT) is presented. A CT scan demonstrated a lesion with faintly increased absorption in the right cerebellopontine angle. Postcontrast CT revealed two discrete areas of homogeneous enhancement. Microscopically, the tumor consisted of a large amount of desquamated keratinized material lined by squamous cell carcinoma. At autopsy, the tumor was found to have invaded the brain stem, in spite of the absence of widespread leptomeningeal infiltration. (10 refs)

- 79-5312 Localized Primary Intracranial Ewing's Sarcoma of the Orbital Roof. Case Report. (Eng)

Alvarez-Berdecia, A. (Section Neurological Surgery, Univ. Puerto Rico, GPO Box 5067, San Juan, Puerto Rico 00936); Schut, L.; Bruce, D. A. *J Neurosurg* 50(6): 811-813; 1979.

A rare case of primary Ewing's sarcoma arising from the intracranial portion of the right orbital roof occurred in a 6-yr-old boy. The patient presented with two rapidly growing tender lumps on his forehead and a 1-yr history of headaches. X-rays showed marked diastasis of the coronal suture and a mottled appearance on the right frontal bone suggestive of sarcoma. Computerized tomography revealed the intracranial extension of the tumor. (19 refs)

- 79-5313 Pseudoepitheliomatous Hyperplasia of the External Ear, Middle Ear, and Mastoid. (Eng) Khan, A. S. (4000 Annapolis Road, Baltimore, MD 21227). *Laryngoscope* 89(6, part 1): 984-987; 1979.

The first known case of pseudoepitheliomatous hyperplasia involving the external ear, middle ear, and the mastoid air cells and labyrinth, resulting from long-standing irrigations with alcohol, is reported. The patient, a 57-yr-old man, presented with persistent pain and chronic discharge from the left ear of 45 yr duration. Recommended treatment had been warm soaks and irrigation with rubbing alcohol (ethyl alcohol for 30 yr, isopropyl alcohol for 15 yr). (7 refs)

- 79-5314 Multiple Intramedullary Neurinomas of the Spinal Cord. Case Report. (Eng) Pardatscher, K. (Inst. Neuroradiology and Neurosurgery, Univ. Padova, Padua, Italy); Iraci, G.; Cappellotto, P.; Rigobello, L.; Pellone, M.; Fiore, D. *J Neurosurg* 50(6): 817-822; 1979.

Multiple neurinomas firmly embedded within the nervous substance of the spinal cord and presumably extending over the entire length of its surface developed in a 41-yr-old man. He had a history of continuous severe pain in the thoracic spine for 6 mo and progressive weakness and paresthesia in the lower limbs, wide gait, sexual impotence, and urinary incontinence for 8 wk. The complete lack of a relationship of the multiple lesions with the spinal nerve roots and the absence of any signs of neurofibromatosis were the most salient features of this rare case. The association of the intramedullary neurinomas with the spinal cord, their distribution along its longitudinal axis, and their histopathological features favor the hypothesis that these lesions are an example of neurocristopathy, a term coined to denote a group of dysgenic, hamartomatous, and neoplastic conditions that have as a common pathogenetic factor a disturbance in the development of the neural crest and in the migration of its cells. (28 refs)

- 79-5315** Glomus Jugulare Tumor Presenting with Increased Intracranial Pressure. Case Report. (Eng) Beck, D. W. (Div. Neurosurgery, Univ. Iowa Hosps. and Clinics, Iowa City, IA 52242); Kassell, N. F.; Drake, C. G. *J Neurosurg* 50(6): 823-825; 1979.

A glomus jugulare tumor presenting with papilledema and visual loss developed in a 51-yr-old obese woman. The tumor was extremely vascular, with significant shunting of arterial blood into venous sinuses. There was no intracranial extension of tumor. The fact that the papilledema and high-amplitude intracranial pulsations resolved after tumor removal strongly suggests that the neoplasm was the causative mechanism. The presence of papilledema in association with such a tumor does not necessarily indicate intracranial extension. (5 refs)

- 79-5316** Neurosurgical Desmoid Tumors. Presentation of Four Cases with a Review of the Differential Diagnoses. (Eng) Friede, R. L. (Dept. Neuropathology, Inst. Pathology, Univ. Zurich, Zurich, Switzerland); Pollak, A. *J Neurosurg* 50(6): 725-732; 1979.

The case reports of four patients (females aged 9, 11, 40, and 67 yr) with desmoid neurosurgical tumors are presented, along with a brief review of the differential diagnoses of intracranial or spinal fibromatous or desmoid lesions. Two of the tumors were identified as densely collagenized meningiomas by their typical ultrastructure. The classification of the other two tumors remains uncertain, but they were thought to belong to the family of desmoid tumors. (34 refs)

- 79-5317** Preferential Digestion of Basement Membrane Collagen by an Enzyme Derived from a Metastatic Murine Tumor. (Eng) Liotta, L. A. (Lab. Pathophysiology, NCI, NIH, Bethesda, MD 20014); Abe, S.; Robey, P. G.; Martin, G. R. *Proc Natl Acad Sci USA* 76(5): 2268-2272; 1979.

The specificity of human skin collagenase and of an enzyme from an invasive tumor were studied with the use of native types I, II, III, IV, and V (AB) collagen as substrates. Human skin collagenase degraded types I, II, and III collagen, producing the characteristic 3/4 and 1/4 cleavage products, but it failed to degrade type IV or V collagen. Collagenase prepared from the invasive tumor showed max activity after trypsin treatment. The tumor enzyme degraded type IV (basement membrane) collagen, producing fragments consistent with a single cleavage site, but it did not attack types I, II, III, and V collagen. Because type IV collagen prepared by pepsinization of placenta was also digested, it is likely that cleavage of type IV collagen by the tumor collagenase occurs within a largely helical domain. A type IV collagenase could play a significant role in tumor

metastases and in normal tissues where basement membrane turnover occurs. Preliminary studies indicate that an enzyme degrading type IV collagen is produced by rat breast ducts and involuting breast tissue in culture. (26 refs)

- 79-5318** Erythroleukemia: In Vitro Studies of Erythropoiesis. (Eng) Newcomb, M. M. (Veterans Admin. Hosp., 1500 E. Woodrow Wilson, Jackson, MS 39216); Balducci, L.; Coleman, M. B.; Steinberg, M. H. *Am J Hematol* 5(4): 291-295; 1978.

The growth of erythroid burst-forming units (BFU-E) and erythroid colony forming units (CFU-E) from the bone marrow and blood of six patients with erythroleukemia and controls with no hematologic disorders was studied. One patient had received several courses of chemotherapy. In the controls, the av number of clusters per BFU was 5.3, while in the patients whose marrow grew BFU-E, the av number was 3.2. When erythropoietin was omitted from patient cultures, no colonies formed. Erythropoietin in excess of 4 units/ml for BFU-E and 2 units/ml for CFU-E did not promote additional colony growth. In controls, BFU-E growth was linear with mononuclear cell inputs of $0.5-2.5 \times 10^5$ /culture with erythropoietin concentrations greater than 2 units/ml; these cultures were routinely incubated with 4 units/ml to assure maximal erythropoietin stimulation. (21 refs)

- 79-5319** Squamous Cell Carcinoma Arising in Chronic Osteomyelitis. (Eng) Inglis, A. M. (Div. Orthopedics, Dept. Surgery, Univ. British Columbia, 2740 Heather St., Vancouver, British Columbia V5Z 314 Canada); Morton, K. S.; Lehmann, E. C. *Can J Surg* 22(3): 271-273; 1979.

The occurrence of squamous cell carcinoma (SCC) in an area of chronic osteomyelitis in three patients is reported. A 49-yr-old man who developed osteomyelitis involving the tibia 40 yr earlier and who had suffered a minor injury to the chronically infected limb 2.5 mo earlier presented with a well-differentiated SCC infiltrating the tibia. This case was atypical in that there had been no sinus drainage from the infected limb for 34 yr prior to occurrence of the tumor. A 72-yr-old man who developed hematogenous osteomyelitis of the right leg at age 12 yr presented with SCC on the anterior aspect of the right leg. A 79-yr-old man presented with a well-differentiated, infiltrating SCC on the plantar aspect of his left heel. This patient had suffered from chronic osteomyelitis dating from an injury sustained 46 yr earlier. The development of SCC in areas of chronic osteomyelitis is chiefly a problem in men of middle age or older. The tibia is the site of infection in 50% of these cases. Prognosis is guarded and the treatment of choice is amputation. (9 refs)

79-5320 Cardiac Sarcoma Causing "ASH" and Stimulating Coronary Heart Disease. (Eng)

Isner, J. M. (Pathology Branch, Natl. Heart, Lung, and Blood Inst., NIH, Bethesda, MD 20014); Falcone, M. W.; Virmani, R.; Roberts, W. C. *Am J Med* 66(6): 1025-1030; 1979.

A primary cardiac sarcoma in a 48-yr-old man preferentially infiltrated the ventricular septum while essentially sparing the left ventricular free wall, resulting in striking echocardiographic and morphologic asymmetry between the septum and the free wall (ie, asymmetric septal hypertrophy). No reports have appeared previously of a patient with an intramural cardiac neoplasm demonstrated by an echocardiogram. Clinically, the patient had features typical of coronary heart disease, yet at necropsy the extramural coronary arteries showed insignificant (<75%) cross-sectional area luminal narrowing by atherosclerotic plaques. (17 refs)

79-5321 Multiple Malignant Spiegler Tumors with Brachydactyly and Racket-Nails. Light and Electron Microscopic Study. (Eng)

Tsambaos, D. (Dept. Dermatology, Univ. Gottingen, 34 Gottingen, W. Germany); Greither, A.; Orfanos, C. E. *J Cutan Pathol* 6(1): 31-41; 1979.

The case report of a 67-yr-old woman with multiple malignant Spiegler scalp tumors coincident with brachydactyly on the fifth fingers and racket nails on all fingers is presented, together with light and electron microscopy findings. The occurrence of similar clinical features in the patient's family suggests a hereditary disorder. The microvillous appearance of the cell surface, the incomplete formation of lumina, the accumulation of small vacuoles, and the existence of secretory granules confirmed the sweat gland origin of the scalp tumors. (16 refs)

79-5322 Diagnosis of Lymphoepithelioma of the Nasopharynx. (Rus) Golovin, D. I. (Sanitary-Hygienic Inst., Leningrad, USSR); Smirnova, I. N. *Vopr Onkol* 25(4): 31-35; 1979.

Current data on the histogenesis of lymphoepitheliomas are critically reviewed. A retrospective analysis of the case histories of 43 patients with lymphoepithelioma of the nasopharynx revealed that 34 patients had in fact had poorly differentiated carcinomas with lymphocytic infiltration and 9 patients had an epithelioid variant of reticulosarcoma. It is strongly emphasized that a differential diagnosis between poorly differentiated carcinomas and reticulosarcomas can be made only by examination of serial sections. A diagnosis of lymphoepithelioma is incorrect, as tumors that consist of a mixture of malignant epithelial and malignant lymphoid cells do not exist. (19 refs)

79-5323 Liver-colonizing Melanoma Cells Selected from B-16 Melanoma. (Eng) Tao, T. (Dept. Biochemistry, Biocenter, 4056 Basel, Switzerland); Matter, A.; Vogel, K.; Burger, M. M. *Int J Cancer* 23(6): 854-857; 1979.

A population of B-16 melanoma cells showing an increased tendency to form tumor nodules in the liver following iv and intraarterial injection was selected in vivo from male C57BL/6 mice. The cells were selected by a stepwise procedure: (1) injection of the original cells through the portal circulation; (2) removal of tumor cells from the hepatic tumor nodules for culture in vitro; (3) reinjection of such cells through the portal circulation and repetition of steps 2 and 3 eight times. The predilection of the selected cells to form tumors in the liver was clearly demonstrated following injection of the cells intraarterially. The accuracy of the injection technique was controlled by monitoring amounts of injected radioactively labeled Sephadex microspheres. This liver-colonizing preference was not exclusive, but relative. (9 refs)

79-5324 Hypercalcemia and Malignant Melanoma. (Eng) Burt, M. E. (Surgery Branch, NCI, Building 10, Bethesda, MD 20014); Brennan, M. F. *Am J Surg* 137(6): 790-794; 1979.

The case reports of two men (aged 26 and 37 yr) with malignant melanoma and hypercalcemia are presented. Of 560 melanoma patients examined between 1970 and 1977, 6 (1.1%) had hypercalcemia. Five of these patients had bone metastases and one had primary hyperparathyroidism and metastatic malignant melanoma with no evidence of bone metastases. Of 804 patients with malignant melanoma examined between 1953 and 1977, 42 (5.2%) had bone metastases; serum calcium was not determined. Of the six hypercalcemic patients in the first series, five were men with a mean age of 45 yr (range, 26-83 yr). The mean serum calcium was 14.6 mg/100 ml and the mean serum phosphorus was 3.8 mg/100 ml. Serum parathyroid hormone determinations in three subjects revealed an elevated level in the patient with primary hyperthyroidism but no detectable activity in two patients with bone metastases. Chloride/phosphate ratios correctly differentiated patients with bone metastases from the patient with primary hyperparathyroidism. (20 refs)

79-5325 The Transformation of Laryngeal Leucoplakia to Cancer. (Eng) Henry, R. C. (Withington Hosp., West Didsbury, Manchester M20 8LR, England). *J Laryngol Otol* 93(5): 447-459; 1979.

The transformation of laryngeal keratosis to cancer is discussed. Keratosis is the keratinization of the stratified squamous epithelium of the true vocal cord. Cellular atypia

denotes not only faulty maturation, but also individual cell alterations. The appearance of the full thickness of the epithelium between the intact basement membrane and the surface occupied by atypical cells with total loss of the cytological architecture is carcinoma in situ. An invasive carcinoma occurs when the basement membrane is disrupted and the malignant cells spread down into the underlying stroma. The progress of laryngeal keratosis was studied in 38 men and 5 women aged 25-80 yr; the highest incidence was in the fifth, sixth, and seventh decades of life. Thirty-four patients were smokers. Thirty-eight patients showed no change from laryngeal keratosis to cancer, although two cases progressed to keratosis with atypia. Five patients developed squamous carcinoma. Four of the carcinomas developed from keratosis with atypia and four were invasive. Reports in the literature have identified 18 carcinomas among 135 cases of keratosis with atypia (13.3%); 12 of these were invasive. Only 3 carcinomas developed in 138 patients with keratosis without atypia. Thus, keratosis with atypia can be considered precarcinomatous. (7 refs)

- 79-5326 An Established Lung Cancer Cell Line Producing Colony-stimulating Activity. (Eng) Kimura, N. (First Dept. Internal Medicine, Faculty Medicine, Kyushu Univ., Higashi-ku, Fukuoka, Japan); Niho, Y.; Ono, J.; Miyamoto, N.; Shibuya, T.; Takaki, R. *Proc Jpn Acad* 54(9): 548-552; 1978.

The establishment of a lung cancer cell line with colon-stimulating activity (CSA) is reported. The cell line was derived from the pleural effusion of a patient (44-yr-old man) with undifferentiated giant cell carcinoma and with a high level of CSA in his serum, urine, and pleural effusion. The degree of proliferation of the cultured cells was low in the early period but became more active after 3 mo. The proliferation pattern of the cancer cells (KONT cells) was epithelial. The cell size was varied and numerous granules were seen in the cytoplasm. KONT cells implanted sc in a nude mouse gave rise to a tumor with the same pattern as the giant cell carcinoma seen in the patient. Thus, the KONT cells originated from giant cell carcinoma. A CSA assay of the supernatant of the KONT cell culture revealed a high level of colony formation in human and mouse marrow cells. The KONT cells should be useful in studying the mechanism of granulopoiesis, since they consistently produce markedly high levels of CSA. (9 refs)

- 79-5327 A 46,XY Lung Adenocarcinoma in a 46,XX Female Patient. A Possible Parental Transmission. (Eng) Genest, P. (Dept. Pathology, Faculty Medicine, Laval Univ., Quebec, Quebec G1K 7P4, Canada); Lagace, R.; Bouillant, A.; Dumas, L.; Bonenfant, J. L. *Acta Cytol (Baltimore)* 23(3): 237-244; 1979.

A cell line with an XY complement isolated from a biopsy of a lung adenocarcinoma in a 46,XX female patient (age 50) was characterized. The morphology and secretory properties of the cultured cells were similar to those of the tumor. Study of the chromosomes of 67 cells from the first subculture showed that 43% were diploid or near-diploid and that the others were heteroploid, with a distribution that ranged from 36 to 113 chromosomes. Karyotype analysis of the diploid cells revealed that they had a 46,XY complement. The characteristics of the Y chromosome were ascertained by Q- and C-banding techniques. Numerous chromosome abnormalities that are usually found in neoplastic cells were observed in the heteroploid cells of the culture. The cellular characteristics and chromosome abnormalities confirmed the malignant nature of the cell line. Blood lymphocyte culture demonstrated that the patient had a normal female karyotype (46,XX). Because she had seven normal children, it is hypothesized that the malignant clone could have originated only through the mechanism of dispermy from her father, who died of presumed lung cancer. The neoplastic cell line with the Y marker may have been repressed until recent factors favored its evolution. (15 refs)

- 79-5328 Bronchogenic Carcinoma with Coexisting Active Pulmonary Tuberculosis in Urban Blacks. (Eng) Solomon, A. (Dept. Radiology, Baragwanath Hosp., Johannesburg, S. Africa); Hurwitz, S.; Conlan, A. A. *S Afr Med J* 55(24): 979-981; 1979.

The occurrence of coexisting lung cancer and active pulmonary tuberculosis in black South Africans was studied. Six patients with radiographic evidence of pulmonary disease and *Mycobacterium tuberculosis* in their sputum were found to have squamous bronchogenic carcinoma (3 patients) or adenocarcinoma (3 patients). The patients, five of whom were men, ranged in age from 40 to 75 yr. One was a heavy smoker, four were moderate smokers, and one was a nonsmoker. All showed extensive local tumor spread, distant metastasis, and poor pulmonary function. It is likely that the cancer in such patients activates dormant tuberculosis. In a population with a high incidence of tuberculosis, the heavy smoker in his fifth decade seems particularly vulnerable to the combined diseases. (12 refs)

- 79-5329 Granular Cell Tumor of the Common Bile Duct. Case Report and Review of Literature. (Eng) Jain, K. M. (535 Centre St., Nutley, NJ 07110); Hastings, O. M.; Rickert, R. R.; Swaminathan, A. P.; Lazaro, E. J. *Am J Gastroenterol* 71(4): 401-407; 1979.

The occurrence of a granular cell tumor in the common bile duct (CBD) of a 46-yr-old black woman is reported. The

patient remained asymptomatic after cholecystectomy and duodenotomy. The resected CBD showed the appearance of a typical benign granular cell tumor and the resected gallbladder showed mild chronic cholecystitis. Granular cell tumor of the CBD appears to be prevalent only among blacks, the seven reported cases having ranged in age from 15 to 46 yr. The laboratory studies in five cases, including the present case, were consistent with the diagnosis of obstructive jaundice and/or cholecystitis. However, the preoperative diagnosis of this tumor is difficult because there are no specific features of this disease. The origin of these tumors remains debatable. Granular cell tumors are usually benign, but cases of local recurrence and sometimes distant metastases have been reported. Patients have done well after local excision. (26 refs)

- 79-5330 **Alpha-1-Antitrypsin Deficiency and Hepatocellular Carcinoma.** (Eng) Kelly, J. K. (Dept. Pathology, Univ. Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, England); Davies, J. S.; Jones, A. W. *J Clin Pathol* 32(4): 373-376; 1979.

Paraffin-embedded neoplastic and nonneoplastic tissue blocks from 42 cases of hepatocellular carcinoma (HCC) and 98 control livers were examined for the presence of globular inclusions of α_1 -antitrypsin (AAT). Intrahepatic AAT globules are considered indicative of an AAT deficiency resulting from the presence of the Pi Z allele. The inclusions were found in the nonneoplastic liver tissue of 2 cases of HCC and in 1/98 control livers, a difference that is not statistically significant. Typical globules of AAT deficiency were not found in HCC cells. However, one-fourth of the HCC's contained cells that showed diffuse cytoplasmic staining for AAT, a pattern also seen in the nonneoplastic livers. (22 refs)

- 79-5331 **Quantitative Determination of Serum Carcinoembryonic Antigen (CEA) Levels in Patients with Digestive Tract Tumors.** (Spa) Richart, C. (Ciudad Sanitaria de la Seguridad Social, Universidad Autonoma de Barcelona, Barcelona, Spain); Ruibal, A.; Monne, J.; Guardia, J. *Rev Esp Enferm Apar Dig* 55(1): 23-30; 1979.

Serum CEA levels were determined in 90 patients with carcinomas of the digestive tract. The sensitivity of the method was 2.5 nanograms (ng)/ml. Serum CEA levels >15 ng/ml were considered positive. The frequency of positive CEA tests was 18/20 patients with colorectal carcinoma with metastases, 9/18 patients with colorectal carcinoma without metastases, 5/5 patients with pancreatic carcinoma with metastases, 5/6 patients with pancreatic carcinoma without metastases, 12/13 patients with gastric carcinoma with metastases, 4/9 patients with gastric carcinoma without metastases, 3/3 patients with esophageal

carcinoma with metastases, 3/3 patients with esophageal carcinoma without metastases, 4/4 patients with carcinoma of the gallbladder and bile ducts with metastases, 0/2 patients with carcinoma of the gallbladder and bile ducts without metastases, and 7/8 patients with peritoneal carcinomatosis. The serum CEA levels exceeded 40 ng/ml in 39 cases: 34 patients with metastases (34 cases), 4 patients with peritoneal carcinomatosis, and 1 patient with pancreatic carcinoma without metastasis. (26 refs)

- 79-5332 **Therapeutic Endoscopy of an Abrikosov's Tumor in the Esophagus.** (Ger) Schroder, G. (Paracelsus-Klinik, Am Natruper Holz 69, D-4500 Osnabruck, W. Germany); Kohlmann, H. W. *Z Gastroenterol* 17(5): 281-286; 1979.

An almost pea-sized polypous tumor of the esophagus was found in a 33-yr-old man during esophagogastroscope for occult hypogastric symptoms. Examination of the biopsy sample revealed the presence of an Abrikosov's tumor. The tumor was removed completely by a diathermy loop. Abrikosov's tumors of the esophagus are very rare; only 11 cases, 10 of them benign, have been reported in the literature. (16 refs)

- 79-5333 **Rapidly Progressive Scleroderma Associated with Carcinoma of the Oesophagus.** (Eng) Mattingly, P. C. (Rheumatology Unit, Nuffield Orthopaedic Center, Oxford, England); Mowat, A. G. *Ann Rheum Dis* 38(2): 177-178; 1979.

The case report of a 70-yr-old woman with rapidly progressive scleroderma and esophageal carcinoma is presented. The rapid progression of the scleroderma suggests that scleroderma may occasionally represent a systemic manifestation of malignancy. (8 refs)

- 79-5334 **Multiple Squamous Carcinomas and the Oesophagus.** (Eng) Solomon, A. (Dept. Radiology, Baragwanath Hosp., Johannesburg, S. Africa); Hunt, J. *S Afr Med J* 55(25): 1028-1030; 1979.

Three rare cases of simultaneously appearing double carcinoma of the esophagus, two of which occurred in a group of 383 esophageal squamous carcinoma patients investigated as part of an epidemiological survey, are reported. All three patients were men aged 48-58 yr. Presenting symptoms included dysphagia, chest and epigastric pain, and wt loss. The double carcinomas were revealed by barium swallow examinations. In two patients, the upper polypoidal lesions were successfully biopsied; radiographic demonstration and direct visualization or palpation confirmed the presence of the lower lesions. The

PATHOGENESIS

radiological features of all lesions included an irregular surface, destroyed mucosa, and bulky eccentric masses invading the esophageal lumen. There was a shouldering effect between the affected and the adjacent esophageal segments. The mucosa between the two lesions was radiologically intact. The double carcinomas may represent a primary carcinoma that has undergone intraepithelial esophageal extension or large, secondary, metastatic deposits. (6 refs)

- 79-5335 A Case of Gastric Cancer Arising from a Heterotopic Pancreas in the Gastric Wall. (Jpn) Miyake, H. (Dept. Radiology, Gifu Univ. Sch. Medicine, Maebashi, Gunma Prefecture 371, Japan); Yamawaki, Y.; Matuura, S.; Doi, H.; Yamamoto, M.; Oohashi, H.; Miyashita, T.; Ikeda, T.; Goto, S. *Gan No Rinsho* 25(6): 634-638; 1979.

A 72-yr-old man with a gastric cancer thought to have originated from a heterotopic pancreas in the gastric wall is reported. The tumor protruded slightly into the gastric lumen, destroying a portion of the mucosal layer. It extended across to the transverse colon, infiltrating the submucosa without destroying the integrity of the mucosa. A consistent pattern of pancreatic acinar cells was seen throughout the interstitial spaces of the tumor tissue. On the basis of the microscopic examination, the patient was thought to have a heterotopic acinar cell carcinoma. (13 refs)

- 79-5336 The Sites of Origin of Gastric Cancers and Ulcers in Relation to Mucosal Junctions and the Lesser Curvature. (Eng) Evans, D. M. (Histopathology Dept., Llandough Hosp., Penarth, Cardiff, Wales); Cleary, B. K. *Invest Cell Pathol* 2(2): 97-117; 1979.

To clarify the much-disputed relationship between peptic ulcers and gastric cancers, a histological mapping procedure was used to study 32 stomachs bearing small cancers and 23 stomachs bearing ulcers. Over 80% of the gastric cancers and peptic ulcers occurred within 2 cm of both a mucosal junction and the lesser curvature. They showed slight differences in their longitudinal relationship to the pyloric junction. There were differential characteristics between the groups of cancers arising at each of the three mucosal junctions. Cancers in the pylorus and cardia were more common in men (male:female ratio, 2.6:1) and were predominantly well-differentiated, whereas those in the intermediate zone were more common in women (1:1.8) and were predominantly undifferentiated. These and other features suggest that gastric cancers should be subdivided according to the junction of origin. (35 refs)

- 79-5337 Carcinoid Diathesis of the Ileum. (Eng) Warner, T. F. (Dept. Pathology, Indiana Univ. Sch. Medicine, 1100 W. Michigan St., Indianapolis, IN 46202); O'Reilly, G.; Power, L. H. *Cancer* 43(5): 1900-1905; 1979.

A total of 108 carcinoids were discovered in the ileum of a 63-yr-old man who presented with colicky pain and vomiting for the previous 24 hr. He had had similar pain intermittently for 10 yr. The clustering and size distribution of the tumor nodules suggest that the phenomenon reflects mucosal metastasis from a dominant parent tumor rather than multicentric neoplastic foci. A predilection for the antimesenteric mucosa was also observed, and it may be related to mucosal lymphatic spread of the carcinoid tumor. (39 refs)

- 79-5338 Ureterosigmoidostomy and Carcinoma of the Colon. (Eng) Pierce, E. H. (Dept. Pathology, Univ. Vermont, Burlington, VT); Zickerman, P.; Leadbetter, G. W. *Trans Am Assoc Genitourin Surg* 70: 92-98; 1979.

Two cases of the association of colon carcinoma (CC) with ureterosigmoidostomy (USS) are described, and 45 literature cases are reviewed. The first patient (52-yr-old man) had a single lesion at the site of active urine flow. The second (31-yr-old man) had a lesion at both anastomotic sites, one benign and one malignant. They were located at the site of a functional and nonfunctional ureteral implant, respectively. The etiology for the development of CC associated with USS seems to be related to the urine. The incidence of CC associated with USS is 500 times greater than that in the normal population, indicating a 5% lifetime risk. The development time of these lesions varies from 6 to 50 yr postoperatively, but the development time is significantly less in patients >40 yr old. The possibility exists that CC may develop in primary sigmoid urinary diversion conduits or in sigmoid internal conduits to either the bladder or bowel. There have been no reports of bowel carcinoma in an ileal urinary diversion. Follow-up evaluation should include examination of stools for blood every 3 mo after 2 yr, excretory urogram yearly after 5 yr, sigmoidoscopy or colonoscopy every 5 yr, and barium enema every 5 yr. If the patient has hematochezia or the excretory urogram demonstrates ureteral obstruction, sigmoidoscopy and colonoscopy should be done. (37 refs)

- 79-5339 A Case of Mucinous Carcinoma of the Descending Colon Associated with *Schistosoma japonicum* Infection. (Jpn) Naito, H. (Second Dept. Surgery, Kurume Univ. Sch. Medicine, Kurume 830, Japan); Isomura, T.; Okabe, M.; Kojiro, M.; Iwamoto, G.; Misoguchi, M. *Gan No Rinsho* 25(4): 325-328; 1979.

A combination of mucinous carcinoma and *Schistosoma japonicum* infection was observed in the descending colon of a 77-yr-old man who presented with an intestinal obstruction. The schistosomiasis was initially diagnosed 20 yr previously. A limited degree of atypical cellular proliferation was seen in the mucosa, but primary tumor involvement occurred in the submucosa, muscle layer, and serosa. Numerous nodules formed by *S. japonicum* ova were observed in the submucosa. Mucin-producing cystic cells that had infiltrated from the serosa were found in the muscle layer. The epithelial cells lining the cysts found in the muscle layer were mixed with atypical epithelial cells of the mucosa in papillary structures. The features of ulcerative colitis associated with *S. japonicum* infection and with colon cancer are reported to be the same. Mucin production is often increased in adenocarcinoma and ulcerative colitis patients. The simultaneous occurrence of increased mucin production, ulcerative colitis, and both cystic and adenocarcinoma cells accompanying the schistosomiasis in this patient is considered significant in linking *S. japonicum* and carcinogenesis. (14 refs)

- 79-5340 Neuroblastoma. Report of One Case. (Ita) Cavaliere, A. (Istituto di Anatomia e Istologia Patologica, Università di Perugia, Perugia, Italy); Bacci, M.; Moretti, A. *Pathologica* 71(1011): 115-119; 1979.

A tumor of the right iliac fossa was found in a 6-mo-old boy. The resected tumor was diagnosed as a Wilms' tumor of the right kidney. Another tumor, interpreted as a local recurrence with mesenteric spread and liver metastasis, developed 3 mo later. At autopsy, this tumor was identified histologically as a large neuroblastoma originating from the sympathetic nervous system. (13 refs)

- 79-5341 Morphologic Classification of Inflammatory, Nonspecific, and Proliferative Lesions of the Urinary Bladder of Mice. (Eng) Frith, C. H. (Pathology Services Project, Natl. Center Toxicological Res., Jefferson, AR 72079). *Invest Urol* 16(6): 435-444; 1979.

A morphologic classification of inflammatory, nonspecific, and proliferative lesions of the mouse urinary bladder was developed based on examinations of approx 75,000 mice. Acute inflammation is characterized by the presence of neutrophils in the lumen and/or mucosa and lamina propria, and chronic cystitis is associated with numerous mononuclear cells infiltrating the lamina propria and/or muscle coat. Nonspecific lesions include vacuolization of the transitional epithelium, squamous metaplasia, crystalluria, urinary calculi, and dystrophic mineralization. Proliferative lesions include simple and papillary hyperplasia of the transitional epithelium; nodular hyperplasia; diverticula, usually of the ureters or urethra; papillary and nonpapillary carcinomas (transitional, transi-

tional with squamous metaplasia, squamous cell, undifferentiated, and adenocarcinoma); infiltrative lesions (stage O, A, B, C, and D); primary mesenchymal tumors (vascular, muscular, fibrous connective tissue, and other); and metastatic tumors. (22 refs)

- 79-5342 Polyps of the Urethra in Children. (Eng) Zachwiej, J. (Urological Clinic, Postgraduate Medical Education Centre, Warsaw, Poland); Witeska, A. *Int Urol Nephrol* 11(1): 49-55; 1979.

The case reports of two boys, aged 12 mo and 15 yr, with urethral polyps are presented. The patients presented with urinary retention or dysuria. In both cases, the polyp was excised along with the peduncle. In the first patient, microscopic examination revealed that the polyp was fibrous and partially covered with transitional epithelium, partially with squamous epithelium. In the second patient, the polyp was of the urethral glandular type. (8 refs)

- 79-5343 Pathogenesis of Colonic Polyps in Multiple Juvenile Polyposis. Report of a Case Associated with Gastric Polyps and Carcinoma of the Rectum. (Eng) Goodman, Z. D. (Dept. Pathology, Johns Hopkins Hosp., Baltimore, MD 21205); Yardley, J. H.; Milligan, F. D. *Cancer* 43(5): 1906-1913; 1979.

The pathogenesis of juvenile polyps of the colon was studied in a 23-yr-old woman with multiple juvenile polyposis who underwent proctocolectomy for rectal carcinoma and antrectomy for associated polyps of the stomach. Numerous polyps up to 3 cm in diameter were present predominantly in the cecum and rectum; in addition, there was an adenocarcinoma in the rectum. Microscopically, there were five categories of lesions: (1) hyperplastic epithelial foci and small hyperplastic polyps; (2) typical juvenile polyps; (3) juvenile polyps with focal adenomatous epithelium; (4) adenomas; and (5) an adenocarcinoma. The five categories could represent a pathogenetic sequence, beginning with epithelial hyperplasia and leading to small hyperplastic polyps that become inflamed and enlarge, forming juvenile polyps. Focal adenomatous areas that develop in some juvenile polyps might give rise to adenomas and, in turn, lead to carcinoma. Although juvenile polyps are generally not considered to be premalignant lesions, this case demonstrates that neoplastic changes may occur in juvenile polyps in certain individuals and it raises the possibility that they may, on occasion, give rise to carcinoma. (9 refs)

- 79-5344 Metastatic Colonization Potential of Primary Tumour Cells in Mice. (Eng) Tarin, D. (Dept. Histopathology, John Radcliffe Hosp., Headington, Ox-

ford, England); Price, J. E. *Br J Cancer* 39(6): 740-754; 1979.

A model has been developed for studying the capability of cells from primary murine mammary tumors to establish colonies in distant organs. The model involves the iv inoculation of disaggregated tumor cells into autologous and syngeneic recipients. There were sharp differences in the colonization potential of primary tumors inoculated into CBA/lac mice: extensive replacement of lung tissue by large colonies of tumor with high colonization potential (HCP) was observed in 37% of the animals; and tumors of low colonization potential (LCP) formed few or no lung colonies (63% of the animals). There was no direct relationship between grade of colonization and survival time in that some animals with Grades IV and V were still alive and apparently well at 90 days. However, there was a tendency for groups with very heavy colonization results to die before the end of the experimental period. There were no characteristic features in common between tumor deposits in organs other than the lungs. The findings in DBA₂ mice were similar to those in CBA/lac animals. The incidence of metastasis from undisturbed murine mammary tumors was less than 2%. There was no correlation between tumor size or morphologic features and colonization potential. Both histologic and electron microscopic observations indicated the mammary origin of the lung tumor tissue. (11 refs)

79-5345 Gonadoblastoma Associated with Malignant Teratoma. (Eng) Luzzatto, R. (Dept. Pathology, Univ. Texas System Cancer Center, MD Anderson Hosp. and Tumor Inst., 6723 Bertner, Houston, TX 77030); Murray, J. M.; Gallager, H. S. *South Med J* 72(5): 624-627; 1979.

Gonadoblastoma associated with malignant teratoma in the contralateral ovary occurred in a 19-yr-old girl. A karyotype of the peripheral blood lymphocytes was 46 XY; there were no individual chromosome abnormalities. The risk of development of a malignant gonadal neoplasm in XY gonadal dysgenesis is sufficiently high to justify prophylactic gonadectomy. (10 refs)

79-5346 Feminizing Thecal-Granulosa Cell Tumor of the Ovary with Pseudopubertas Praecox. (Spa) Vinuela, A. (Residencia Sanitaria de la S. S. "Virgen Blanca", Leon, Spain); Manero, S.; Toyos, J. M.; Fernandez-Rojo, F.; Martinez-Merino, A. *Tokoginecol Pract* 37(414): 89-104; 1978.

An ovarian tumor was suspected in an 8-yr-old girl showing signs of pseudopubertas praecox. She presented with acute abdomen, abdominal tumor, and oliguria. A pedicled tumor of the right ovary was found. Right salpingo-oophorectomy was performed. The estrogen levels were

normal 31 mo after the surgery, at which time the patient had not yet reached puberty. The tumor was identified histologically as a unilateral, feminizing, thecal granulosa cell tumor of the macrofollicular and microcystic type, with predominant thecal elements. There were no Call-Exner bodies or massive edema in the stroma, but the tumor did show signs of luteinization. (45 refs)

79-5347 Familial Carcinoma of the Ovary: Case Report. (Eng) Philipp, E. E. (Royal Northern Hosp., London, England). *Br J Obstet Gynaecol* 86(2): 152-153; 1979.

The case report of a 53-yr-old woman who developed a poorly differentiated cystadenocarcinoma of the ovary is presented. Family history revealed that of 10 women at risk in two generations, 5 (including this patient) had developed ovarian carcinoma. They were the patient's mother, her mother's sister, that sister's daughter, and another maternal aunt's daughter. (11 refs)

79-5348 Five Metachronous Malignant Neoplasms: A Follow-up Report. (Eng) Russell, J. M. (Dept. Surgery, Section Urology, North Carolina Baptist Hosp., Winston-Salem, NC 27103); Myers, R. T.; Harrison, L. H. *NC Med J* 40(5): 284-285; 1979.

The case report of a 66-yr-old woman who had five separate sequential malignancies over a 17-yr period is presented. She had an adenocarcinoma of the uterus, transitional cell carcinoma of the left renal pelvis and ureter, transitional cell carcinoma of the right ureter, adenocarcinoma of the transverse colon, and adenocarcinoma of the hepatic flexure. The cause of the increased susceptibility is unclear, although a defect in immunologic surveillance must be considered. (12 refs)

79-5349 A Woman with Acanthosis Nigricans Maligna, a Paraneoplastic Syndrome. (Dut) Oranje, A. P. (Afdelingen Dermatologie, Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam, Netherlands); Smit, A. F.; Vuzevski, V.; Stolz, E. *Ned Tijdschr Geneesk* 123(19): 789-791; 1979.

An 81-yr-old woman developed acanthosis nigricans maligna in the lips and in the axilla about 4.5 mo after hysterectomy for a moderately differentiated endometrial adenocarcinoma. No virus particles were found in the biopsy specimen from the lip. The patient died of the adenocarcinoma; acanthosis nigricans disappeared during the terminal stage. (11 refs)

- 79-5350 A Further Cytogenetic Study of Hydatidiform Mole, with Reference to its Androgenetic Origin. (Eng) Wake, N. (Dept. Obstetrics and Gynecology, Sch. Medicine, Hokkaido Univ., Sapporo, Japan); Shiina, Y.; Ichinoe, K. *Proc Jpn Acad* 54(9): 533-537; 1978.

A cytogenetic analysis was performed on six hydatidiform mole conceptuses and their parents. Molar tissues were removed from the uterine cavity and cultured in minimal essential medium supplemented with 20% fetal calf serum in 5% carbon dioxide in air. The six cases were characterized by a normal female karyotype (46,XX), and their parents were also chromosomally normal. Six pairs of marker chromosomes (3, 13-15, 21-22) were scored for Q-band polymorphism. The Q-banded chromosomal features in cells from the six moles had uniform homozygosity in members of each pair, but the parental karyotypes had at least one pair that was heterozygous. With one exception, neither of the maternal homologs was transmitted to moles in 10 identified pairs of chromosomes; while both members of 8 homologs identified in moles were traceable only to one of the corresponding paternal homologous chromosomes. These findings suggest that the moles received a paternal haploid set in duplicate, but none from the mother. The chromosomes from four primary and metastatic chorionic tumors were investigated recently. They were characterized by a high incidence of cells in the tetraploid range, and the homologous chromosomes of certain pairs with polymorphic chromosome variants were not morphologically identical. These findings do not support the view of cellular continuity between moles and choriocarcinoma. (12 refs)

- 79-5351 Sarcoma of the Vulva. (Fre) Guerard, M. J. (Departement de Pathologie, Hopital Notre-Dame, Montreal, Canada); Paquin, F.; Audet-Lapointe, P.; Charbonneau, A. *Union Med Can* 108(5): 501-505; 1979.

A 48-yr-old woman developed a rapidly growing tumor in the labium majus. She developed a recurrence 2 yr after simple resection. The tumor was diagnosed as a leiomyosarcoma of the vulva. Radical vulvectomy and lym-

phadenectomy were performed. The resected lymph nodes were free from metastasis. This is the seventh case of vulvar leiomyosarcoma reported in the literature. (24 refs)

- 79-5352 Simultaneous Prostatic Carcinoma and Genital Paget's Disease Associated with Subjacent Adenocarcinoma. (Eng) Oka, M. (Dept. Urology, Kumamoto Chuo Hosp., 1-16-1, Shinyashiki, Kumamoto 862, Japan); Saita, B.; Nakashima, K. *Br J Urol* 51(1): 49; 1979.

The case report of a 65-yr-old man with prostatic carcinoma and extramammary Paget's disease of the scrotal skin is presented. In addition, nests of adenocarcinoma were found in the dermis of the scrotum underneath the Paget's cells. (3 refs)

See also:

- *(Rev.): 79-4801, 79-4829, 79-4832, 79-4835, 79-4840, 79-4846, 79-4847, 79-4881, 79-4899, 79-4901, 79-4908, 79-4909, 79-4910, 79-4911, 79-4912, 79-4913, 79-4914, 79-4915, 79-4916, 79-4917, 79-4922.
- *(Chem.): 79-4941, 79-4945, 79-4946, 79-4957, 79-4960, 79-4964, 79-4971, 79-4972, 79-4978, 79-4980, 79-4981, 79-4982, 79-4994, 79-4995, 79-4996, 79-4998, 79-5002, 79-5006, 79-5013, 79-5017, 79-5036, 79-5042, 79-5043, 79-5064, 79-5076, 79-5079, 79-5083, 79-5086.
- *(Phys.): 79-5096, 79-5097, 79-5101, 79-5102, 79-5103, 79-5104, 79-5107, 79-5108, 79-5109, 79-5112, 79-5113, 79-5114.
- *(Viral): 79-5119, 79-5121, 79-5149, 79-5172, 79-5182, 79-5184, 79-5222, 79-5233.
- *(Immun.): 79-5247, 79-5249, 79-5252, 79-5260, 79-5266, 79-5267, 79-5269, 79-5272, 79-5275, 79-5280.
- *(Epid.-Biom.): 79-5365, 79-5367, 79-5368, 79-5377, 79-5382, 79-5390.

EPIDEMIOLOGY AND BIOMETRY

- 79-5353 Sequential Pathogenic Components of Rates. (Eng) Morrison, A. S. (Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA 02115). *Am J Epidemiol* 109(6): 709-718; 1979.

A relationship was derived between rates of sequential pathogenic transitions and the corresponding overall rate of disease. The av duration of the entire natural history of a disease is the sum of the average durations of all of its stages. The rate of termination of each stage is inversely related to the duration of the stage; the overall rate for a disease with multiple stages is the reciprocal of the total average duration of the natural history. The overall rate for multiple stages must be less than the lowest component transition rate. Thus, for any particular disease, the mortality rate is less than both the incidence rate among the well and the rate of death among the diseased. The incidence rate is less than both the rate of preclinical disease development and the rate of transition from preclinical disease to clinical. A change in the rate of one transition, such as that of cancer initiation, will be underestimated by the corresponding change in and overall rate such as the incidence rate. Similarly, a change in an incidence rate will be underestimated by the respective change in the overall mortality rate. The max change in an overall rate due to any degree of change in one transition rate is limited by the size of other rates in the sequence. (16 refs)

- 79-5354 Estrogen Replacement Therapy II: A Prospective Study in the Relationship to Carcinoma and Cardiovascular and Metabolic Problems. (Eng) Nachtigall, L. E. (Dept. Obstetrics and Gynecology, New York Univ. Medical Center, New York, NY 10016); Nachtigall, R. H.; Nachtigall, R. D.; Beckman, E. M. *Obstet Gynecol* 54(1): 74-79; 1979.

A 10-yr double-blind prospective study was undertaken to evaluate the effects of estrogen replacement therapy (ERT). The sample population consisted of 84 pairs of randomly chosen postmenopausal in-patients, matched for age and diagnosis. The treatment group received conjugated estrogen (Premarin: 2.5 mg/day) and medroxyprogesterone acetate (Provera: 10 mg/day) for 7 days in each month; the controls received placebos. The results revealed no statistically significant difference in the incidence of thrombophlebitis, myocardial infarction (MI), or uterine cancer. There was a lower incidence of breast cancer in the treated group. The estrogen-treated patients had a higher incidence of cholelithiasis. Those in the

treated group who began the study with elevated beta/alpha lipoprotein ratios showed a reduction in that ratio over the course of the study. In the control group, these ratios remained constant or increased. The low number of cases precludes drawing any real significance from the data on diseases of low frequency. The study excludes only a high incidence of complications from estrogens. (26 refs)

- 79-5355 Multiple Malignancies in Patients with Primary Carcinomas of the Head and Neck. (Eng) Weichert, K. A. (Dept. Radiotherapy, Univ. Cincinnati Coll. Medicine, Cincinnati, OH 45267); Schumrick, D. *Laryngoscope* 89(6, part 1): 988-991; 1979.

Of 825 patients with primary carcinomas of the head and neck registered with the Head and Neck Tumor Services at the University of Cincinnati Medical Center Affiliated Hospitals, 54 had multiple primaries. Synchronous lesions occurred in 19, nonsynchronous lesions in 35. The secondary tumor sites were the head and neck (33), lung (12), esophagus (4), and rectum, prostate, stomach, and breast (5). All 54 patients had continued to drink or smoke after the original diagnosis, leading to the conclusion that as long as the carcinogenic agent (alcohol/tobacco) continues to be present, the patient will continue to be affected. (12 refs)

- 79-5356 Chronic Alcoholism and Subsequent Mortality in World War II Veterans. (Eng) Robinette, C. D. (Medical Follow-up Agency, Natl. Academy Sciences-Natl. Res. Council, 2101 Constitution Ave., Washington, DC 20418); Hrubec, Z.; Fraumeni, J. F. *Am J Epidemiol* 109(6): 687-700; 1979.

Mortality during 1946 through 1974 among 4,401 US Army servicemen hospitalized for chronic alcoholism in 1944-1945 was compared with that of individually age-matched subjects hospitalized for nasopharyngitis. The relative risk of death from all causes for the alcoholism vs the nasopharyngitis admissions was 1.87 ($p < 0.001$). The relative risks were significantly high for death due to alcoholism (12.8), tuberculosis (10.2), alcoholic cirrhosis (3.5), trauma (3.1), nonmalignant diseases of the esophagus, stomach, and duodenum (2.5), ill-defined causes of death (2.1), nonmalignant respiratory diseases including pneumonia (1.7), and ischemic heart disease (1.4). A significant excess risk was also noted for brain cancer

and for diseases of the liver or gallbladder (other than cancer or cirrhosis), but relative risks could not be estimated because no deaths occurred in the nasopharyngitis group. The risk for all cancers combined was significantly related to alcoholism (1.6, $p < 0.01$) only among subjects discharged to duty or separated from service for disability, and not among those separated administratively for having undesirable character traits. (34 refs)

- 79-5357 Patterns of Incidence of Brain Tumors in Children. (Eng) Gold, E. B. (Dept. Epidemiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD 21205); Gordis, L. *Ann Neurol* 5(6): 565-568; 1979.

A population-based community-wide study of the incidence of brain tumors in children during 1960-1974 was conducted in the Baltimore area. Incidence rates in boys declined over the study period, and the rates were higher in whites than in blacks in all age groups except children < 5 yr. A peak in incidence rates was observed in white 5- to 9-yr-olds and in blacks from 0 to 4 yr of age. In addition, incidence rates tended to be higher in boys than in girls at all ages except puberty (the 10- to 14-yr-old age group) when rates in girls exceeded those in boys. The findings suggest that both host and environmental factors may be involved in the development of brain tumors in children. (13 refs)

- 79-5358 Leukemia in Benzene Workers. (Eng) Infante, P. F. (Industry-wide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Center Disease Control, Cincinnati, OH 45202); Rinsky, R. A.; Wagoner, J. K.; Young, R. J. *J Environ Pathol Toxicol* 2(5, Special): 251-257; 1979.

Workers occupationally exposed to benzene during 1940-1949 at two Ohio plants were followed for vital status up to 1975. In comparison with two control populations, a significant ($p < 0.002$) excess of leukemia was observed. The study population had a fivefold excessive risk of all leukemias and a tenfold excess of deaths from myeloid and monocytic leukemias combined, compared with controls. These figures underestimate the true leukemia risk to benzene-exposed workers, because follow-up was only 75% complete and the untraced 25% were all regarded, in the statistical analysis, as being alive at the end of the study period. The environment of the workers in the study population was not contaminated with solvents other than benzene, and existing records indicate that the benzene levels themselves were generally below the limits recommended at the time they were measured. (22 refs)

- 79-5359 Leukemia from Atomic Fallout (Letter to Editor). (Eng) Bader, M. (2305 N.W. 94th Street, Seattle, WA 98117). *N Engl J Med* 300(26): 1491-1492; 1979.

Mortality from childhood leukemia in Seattle-King County, Washington varied considerably between 1950 and 1972. Only 27% of children studied in a review of leukemia in Washington state from 1956-1961 were ever exposed to x-rays, and most of these exposures were minimal. Evaluation of age-specific leukemia death rates for children in Utah showed no increases in mortality and no distinct relation to radioactive fallout over Utah at any time since 1950. It is suggested that a previous study proposing an association between childhood leukemia and fallout from nuclear testing represents an overinterpretation of limited data. (no refs)

- 79-5360 Pregnancy, Breast-Cancer Risk, and Maternal-Fetal Genetics (Letter to Editor). (Eng) Janerich, D. T. (Bureau Cancer Control, New York State Dept. Health, E.S.P. Tower Building, Albany, NY 12237). *Lancet* 1(8128): 1240-1241; 1979.

Epidemiological data supporting the hypothesis that immune suppression during pregnancy increases the risk of breast cancer (BC) in the short run and decreases it in the long run are defended. Reexamination of current registry data by 1-yr intervals shows that until 40 yr of age, there is a lower proportion of single women among BC cases compared with other cancers. After age 40, the excess begins to appear. In terms of age-specific rates and proportions of single women, there is evidence of a cross-over of incidence associated with marital status for women in their mid- to late 30's that is presumably pregnancy-related. (2 refs)

- 79-5361 Mortality Patterns among Workers in a Gray Iron Foundry. (Eng) Decoufle, P. (Environmental Epidemiology Branch, NCI, 3C07 Landow Building, Bethesda, MD 20014); Wood, D. J. *Am J Epidemiol* 109(6): 667-675; 1979.

The long-term mortality experience of 2,861 men employed for at least 1 mo during 1938-1967 in a US gray iron foundry was examined. Both white and nonwhite workers experienced favorable mortality for most major disease categories compared with the general population rates, even men employed ≥ 5 yr. No deaths from pneumoconiosis were observed, and there were no excess deaths from other chronic respiratory diseases. Analysis of detailed cancer sites showed no significant departures from expected overall values. However, in the subgroup of men who were employed ≥ 5 yr prior to 1938, a twofold increase in mortality from digestive cancer (14 observed deaths vs 7.4 expected) and respiratory cancer (8 observed deaths vs

4.0 expected) was seen. The absence of information on specific foundry jobs held by the subjects and on associated exposures limits full interpretation of the findings. However, the excess observed for respiratory cancer among long-term employees followed for 30 yr is consistent with previous reports. (27 refs)

79-5362 Patterns and Determinants of Conjugated Estrogen Use. (Eng) Rosenberg, L. (Drug Epidemiology Unit, Boston Univ. Medical Center, 10 Moulton St., Cambridge, MA 02138); Shapiro, S.; Kaufman, D. W.; Slone, D.; Miettinen, O. S.; Stolley, P. D. *Am J Epidemiol* 109(6): 676-686; 1979.

The ambulatory use of conjugated estrogens (CE's) in the Greater Boston area is described based on data collected from hospitalized women. In addition, geographic and temporal variation in use was evaluated using prescription survey data from various areas of the US. Among 1,273 women aged 30-69 yr of age interviewed in Greater Boston hospitals, there were 161 ever-users of CE's; 88 had used the drug within the preceding year. The median duration of use was 3 yr. Prominent determinants of use were age, menopause, and history of menopausal symptoms. Physician prescription survey data from an independent source suggest that CE use has been common throughout the US, and that it may have declined after reports linking CE's to endometrial cancer were published in 1975. If CE use indeed increases the risk of endometrial cancer some fivefold, an important public health problem exists. (20 refs)

79-5363 Mortality Patterns among Miners and Millers of Non-asbestiform Talc: Preliminary Report. (Eng) Selevan, S. G. (Industry-Wide Studies Branch, Div. Surveillance Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Rockville, MD 20857); Dement, J. M.; Wagoner, J. K.; Froines, J. R. *J Environ Pathol Toxicol* 2(5, Special): 273-284; 1979.

Mortality and environmental assessments were made of workers exposed to talc free of asbestos and of significant quantities of free silica. This population was drawn from Vermont Health Department records of employees of five companies in three geographic locations. Mortality patterns were assessed from January 1, 1940, through December 31, 1975, and cause-specific expected numbers of deaths were calculated from white male rates for the US and Vermont, using a modified life table technique. Excess nonmalignant respiratory disease mortality was observed in millers, a group thought to have greater lifetime dust exposures than miners. No such excess was observed among miners. Excess lung cancer mortality was observed in the miners, but expected deaths were small and exposures other than talc are suspect for this excess. Past talc exposure

levels often far exceeded the present Occupational Safety and Health Administration and the Mining Enforcement and Safety Administration Standard of 20 mppcf for non-fibrous talc (<1% free SiO₂). Analyses of current airborne dust samples and talc bulk samples showed talcs from all locations in the currently operating mines and mills studied to be similar in composition. No asbestos was detected in any of the samples analyzed by x-ray diffraction or electron microscopy. Levels of free silica in bulk samples were <0.25% for nearly all samples, and only in occasional air samples was free silica detectable. Talc shards and ribbons were seen in talc bulk and airborne dust samples. In addition to talc, other minerals present in these ores in significant quantities included magnesite, chlorite, and dolomite and to traces of calcite, biotite, ankerite, and phlogopite. (26 refs)

79-5364 A Preliminary Report of Mortality Patterns among Foundry Workers. (Eng) Egan, B. (Div. Surveillance, Hazard Evaluations and Field Studies, Industry-wide Studies Branch, Natl. Inst. Occupational Safety and Health, Cincinnati, OH 45202); Waxweiler, R. J.; Blade, L.; Wolfe, J.; Wagoner, J. K. *J Environ Pathol Toxicol* 2(5, Special): 259-272; 1979.

A proportional mortality study of US foundry workers was conducted utilizing the death records maintained from 1971 to 1975 by the International Molders and Allied Workers Union as part of a death benefits program. Death certificates were obtained for 3,013 members of the study group and classified by a trained nosologist. The age- and race-specific cause distribution of all deaths among men in the US for 1973 was used as a standard from which expected deaths were calculated. The statistical significance of differences between observed and expected numbers of deaths was determined by a chi-square test. The most statistically significant finding was an excess lung cancer mortality (208 observed vs 142 expected) and an excess mortality due to pneumoconiosis (29 observed vs 5 expected). Potential agents found in the foundry environment that may be responsible for the increased lung cancer risk include aromatic hydrocarbons, polynuclear aromatic hydrocarbons, nitrosamines, bis(chloromethyl)ether, talc, and asbestos. (21 refs)

79-5365 Effects of Tobacco Smoking and Other Irritating Factors on the Laryngotracheal Mucosa. (Pol) Chodynicky, S. (Klinika Otolaryngologiczna, Instytut Chorob Nerwowych i Narzadow Zmyslow Ak. Med., ul. Parkowa 14 m. 70, 15-224 Bialystok, Poland); Tupalska, M. *Wiad Lek* 32(5): 299-304; 1979.

Epidemiological, clinical, and morphological studies of the epiglottis and trachea were performed in 100 patients (99 men, 1 woman aged 35-59 yr) operated on for laryngeal

carcinoma. The carcinoma was located in the supraglottic part of the larynx in 76 patients, in the glottis in 24. Ninety-six patients were cigarette smokers: 81% had been smoking for >30 yr, the others >20 yr. Forty percent of the smokers smoked 30-40 cigarettes/day, the others more than 20. Ninety-two patients were also exposed occupationally to irritating factors involved in construction work, manufacture of machinery, transportation, and agriculture. Morphological investigations revealed multilayered squamous cell epithelium in the epiglottis. The tracheal mucosa showed signs of inflammation, epithelial damage, and transformation of multilayered columnar epithelium into multilayered squamous epithelium. Atypical cells were also found in some patients. (23 refs)

- 79-5366 Influence of 3,4-Benzopyrene in Falling Dust on the Incidence of Neoplastic Diseases of the Respiratory System in Inhabitants of the City of Szczecin. (Pol) Pilawska, H. (Zaklad Higieny, Pomorska Akademia Medyczna, Szczecin, Poland); Skucinski, S.; Soroka, M.; Rymgayllo, B. *Ochrona Powietrza* 2: 29-34; 1979.

Correlations between the tar and 3,4-benzopyrene (BP) content of falling dust and the incidence of neoplasms of the respiratory tract were studied in Szczecin during a 12-mo period (1975-1976). The dustfall (in ton/km²) as well as the tar and BP content of the dust showed considerable variation in time and space; the dustfall was highest in the summer, the tar and BP content of the dust in the winter. The tar content in the dust ranged from 4.3 to 122.1 mg/g, and the BP content from 0.085 to 0.654 mg/g, averaging 0.256 mg/g for all 10 monitoring sites representing 10 areas of the city. The comparison of the tar and BP levels in the dust with the incidence of neoplasms of the respiratory tract showed no correlation; there was no increase in the incidence in the areas with the highest exposure to BP. (12 refs)

- 79-5367 Some Aspects of Suberosis--A Respiratory Disease Affecting Cork Industry Workers. (Por) Avila, R. (Clinica Universitaria de Doenca Pulmonares, Hospital de Santa Maria, Lisbon, Portugal). *Hisp Med* 36(417): 103-132; 1979.

A detailed study of suberosis in cork industry workers is presented. The association of suberosis with alveolar cell carcinoma was found in a 53-yr-old man who had been working at a cork processing plant for 13 yr and who smoked about 15 cigarettes a day for 30 yr. Cork particles were found in the lung carcinoma. (no refs)

- 79-5368 Lung Cancer in Malaysia. (Eng) Menon, M. A. (Dept. Medicine, Univ. Hosp., Kuala Lumpur, Malaysia); Saw, H. S. *Thorax* 34(2): 269-273; 1979.

Between 1967 and 1976, 388 lung cancer patients were seen at the University Hospital, Kuala Lumpur, 72% of whom had histological confirmation of their disease. Most were aged 50-80 yr, and the male:female ratio was 2.8:1. The patients were predominantly of Chinese origin (82%) and from the lower socioeconomic strata. A history of smoking was elicited in 78%. Only 2% were asymptomatic; 70% presented with a history of <6 mo duration. Most had cough, hemoptysis, wt loss, and dyspnea. The chief radiological features and the diagnostic methods are presented. The various histological types included squamous carcinoma (34%), adenocarcinoma (25%), large cell carcinoma (12%), small (oat) cell carcinoma (12%), "undifferentiated/anaplastic" carcinoma (15%), and others (2%). Malays appeared to have a higher percentage of adenocarcinoma. A comparison between the histologically confirmed group and the remaining patients showed no significant differences in features. (12 refs)

- 79-5369 Occupational Lung Cancer. (Nor) Kreyberg, L. (Munkedamsveien 79, Oslo 2, Norway). *Tidsskr Nor Laegeforen* 99(12): 570-574; 1979.

Epidemiological data on lung cancer in Norway are presented, and the contributions of occupational hazards and smoking to lung cancer are discussed. In the urban male population of Norway, the yearly lung cancer mortality rate was 2/100,000 population in the mid-1930's, 25 in the mid-50's, and 50 in the mid-70's. In the rural male population, the mortality was 2/100,000 in the mid-30's, 5 in the mid-50's, and 20 in the mid-70's. This increase paralleled an increase in the percentage of smokers in the rural population. While exposure to asbestos, uranium, and chromium increases the risk and incidence of lung cancer, smoking habits are also a factor. Thus, incidence and mortality rates are influenced not only by working conditions, but also by the specific smoking habits of individual occupational groups. Considerable differences were found between different occupational groups with regard to the percentages of smokers, the amount of tobacco used per day, and the ratio of cigarette smokers to pipe smokers. In groups with no, or negligible, exposure to specific occupational carcinogens, lung cancer incidence increased with an increase in the percentage of smokers, in tobacco consumption, and in the ratio of cigarette to pipe smokers. The relative risk of lung cancer was calculated to be 1.4 for nonsmokers exposed to asbestos, 12 for smokers without asbestos exposure, and 17 for smokers exposed to asbestos. (14 refs)

- 79-5370 No Lung Cancer in Schizophrenics (Letter to Editor)? (Eng) Coakley, D. V. (55 Rodney Street, Liverpool 1, England). *Br J Psychiatry* 134: 649; 1979.

Over a 5-yr period, eight cases of lung cancer in schizophrenics were confirmed in the postmortem records of a single hospital. Histologically, the tumors were oat cell carcinomas, poorly differentiated squamous carcinomas, and a well-differentiated papillary adenocarcinoma. (no refs)

- 79-5371 Carcinoma of the Lung in Lancashire Coalminers. (Eng) Rooke, G. B. (Pneumoconiosis Medical Panel, Manchester, England); Ward, F. G.; Dempsey, A. N.; Dowler, J. B.; Whitaker, C. *J. Thorax* 34(2): 229-233; 1979.

The incidence at death of lung carcinoma in coal miners and exminers was compared in those with and without pneumoconiosis (PC) at necropsy. Of the 1,003 deaths analyzed, 114 cases of lung carcinoma were found, an incidence (11.4%) no greater than that in the male population in Northwest England. Lung carcinoma was present in 62 (13.1%) of the miners and exminers without PC and in 52 (9.8%) of those with PC. The mean age at death of those with PC was 71.3 yr, so they did not die before the age at which they would have developed carcinoma. Miners and exminers with progressive massive fibrosis whose mean age at death was 72 yr had the lowest prevalence of lung carcinoma at all ages, 8.4%. For reasons stated in the text, this is inevitably a biased sample. The number of those without PC is probably lower than the true figure, because the deaths of miners and exminers in whom there was no suspicion of lung disease may not have been reported to the coroner or to the PC medical panel. There appears to be no positive link between lung carcinoma and PC. There was a surprisingly high number of smokers and exsmokers among the miners, and this finding appears to have more relevance to the incidence of lung carcinoma in this group than does PC. (15 refs)

- 79-5372 Variations in the Incidence and the Spatial Distribution of Patients with Primary Acute Pancreatitis in Nottingham 1969-76. (Eng) Bourke, J. B. (Dept. Surgery, General Hosp., Nottingham NG1 6HA, England); Giggs, J. A.; Ebdon, D. S. *Gut* 20(5): 366-371; 1979.

During 1969-1976, 214 patients with primary acute pancreatitis were admitted to hospitals in the Nottingham, England area. In one patient, pancreatic carcinoma was an etiological factor. An analysis of the distribution of pancreatitis patients according to six water supply areas showed that the number of patients from a particularly hard water area was significantly greater than could have occurred by chance. (28 refs)

- 79-5373 Epidemiology of Cancer of the Pancreas. (Fre) Audigier, J. C. (Centre d'Epidemiologie du CNRS LP 005440, Faculte de Medecine, avenue Rockefeller, 69373 Lyon Cedex 2, France); Lambert, R. *Ann Gastroenterol Hepatol (Paris)* 15(3): 159-162; 1979.

The pancreatic cancer mortality rate in France is 6/100,000 men and 3/100,000 women, and it accounts for 3% of the overall cancer mortality. An increased incidence of pancreatic cancer was seen in cigarette smokers, diabetics, and workers exposed to β -naphthylamine and benzidine. Methylnitrosourea, methylnitrosourea, 2,2'-dihydroxy-N-propylnitrosamine, and 7,12-dimethylbenz(a)anthracene induced pancreatic cancer in experimental animals. (27 refs)

- 79-5374 Primary Liver Tumors Due to Estrogen-Progestogen Preparations: Results of an Open Survey in France. (Fre) Rauber, G. (Laboratoire d'Anatomie Pathologique, CHU de Brabois, route de Neufchateau, F 54500 Vandoeuvre, France); Meot, B. *Nouv Presse Med* 8(23): 1945; 1979.

A tumor registry was established in 1978 to record primary liver tumors associated with the use of estrogen-progestogen compounds. Among women aged 15-50 yr seen by 315 participating French physicians since January 1975, 26 cases, including 2 malignant tumors, were recorded as of March 1979. (1 ref)

- 79-5375 An Epidemiological Study of Hepatic Tumor Incidence in Subjects Working with Trichloroethylene. I. Negative Results of Retrospective Investigations in Subjects with Primary Liver Carcinoma. (Cze) Novotna, E. (Centrum hygieny prace a nemoci z povolani, Institut hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia); David, A.; Malek, B. *Prac Lek* 31(4): 121-123; 1979.

Fifty-six patients with primary liver carcinoma were investigated retrospectively for occupational exposure to trichloroethylene. The patients included 39 men (av age 69 yr) and 17 women (av age 56 yr). The analysis failed to reveal a history of trichloroethylene exposure in any of the subjects. One patient had been exposed to radioactive substances in a watch factory. (6 refs)

- 79-5376 An Epidemiological Study of Hepatic Tumor Incidence in Subjects Working with Trichloroethylene. II. Negative Results of Retrospective Investigations in Dry Cleaners. (Cze) Malek, B. (Hygienicka stanica hl. m. Prahy, Rytirska 12, 110 00 Prague 1, Czechoslovakia); Kromarova, B.; Rodova, O. *Prac Lek* 31(4): 124-126; 1979.

The incidence of primary liver cancer was studied in 57 dry cleaners who had been exposed to trichloroethylene (TCE) for 1-35 yr (60% for >5 yr). The age of the subjects ranged from 25 to 85 yr, with 80% aged >45 yr. The exposure of the subjects to TCE was considerable: urinary trichloroacetic acid concentrations exceeded 100 mg/liter in 60% of those tested, and concentrations up to 1,000 mg/liter were found sporadically. No case of liver cancer was found in this group, but cancers of other organs were found in six men aged 58-75 yr (length of exposure 3-34 yr). This incidence corresponds to the incidence of cancer in this age group in general. Three patients had lung cancer, one had carcinoma of the palate and tongue, one had rectal carcinoma, and another had carcinomas of the urinary bladder and rectum. (1 ref)

- 79-5377 Primary Malignant Lymphoma of the Stomach, Analysis of 38 Cases. (Ger) Klaiber, H. (Pathologisches Institut, Kantonsspital Winterthur, Winterthur, Switzerland); Sulser, H.; Ruttner, J. R.; Kobler, E.; Deyhle, P. *Schweiz Med Wochenschr* 109(18): 668-675; 1979.

A retrospective analysis of 38 cases of malignant lymphoma of the stomach is presented. The patients included 18 men and 20 women. Lymphocytic lymphomas were diagnosed in 3 men and 3 women (av age 56 yr), lymphoblastic lymphomas in 2 men and 4 women (av age 54 yr), mixed-cell lymphomas in 4 men (av age 58 yr), reticulum-cell lymphomas in 7 men and 13 women (av age 63 yr), and Hodgkin's disease in 2 men (av 48 yr). There were no significant differences in symptomatology between lymphoma and carcinoma of the stomach. However, signs of stenosis were missing in the lymphoma patients, even though most of the tumors were located in the antrum. Due to the extreme tendency of the lymphomas to ulcerate (89%), the mean duration of symptoms was only 2.5 mo. Diffuse infiltrative growth was seen in most cases; the tumor extended to the serosa in 19 cases. Tumor size, determined in 35 cases, averaged 7.5 cm. Half of the patients had clinical stage I E at the time of operation. The prognosis was generally best for lymphocytic lymphoma and worst for reticulum-cell lymphoma and lymphoblastic sarcoma. (34 refs)

- 79-5378 Clinicopathological Study of 180 Patients with Early Gastric Cancer. (Jpn) Naito, H. (Second Dept. Surgery, Kurume Univ. Sch. Medicine, Kurume, Fukuoka Prefecture 830, Japan); Kasahara, Y.; Komura, T.; Miyoshi, A.; Nakayama, Y.; Kunitake, K.; Yoshida, K.; Nakayama, T.; Isomura, T.; Okabe, M.; Arakawa, M.; Kojiro, M. *Gan No Rinsho* 25(6): 583-591; 1979.

A total of 180 patients with early stage gastric cancer were classified by Nakamura's system. There were 108 cases of

differentiated cancer in 101 patients (29 women, 72 men; av age 59.9 yr) and 79 cases of undifferentiated cancer in 79 patients (42 women, 37 men; av age 49.9 yr). The differentiated cancers usually occurred on the antrum or on the medial part of the stomach, and they were either protruded or depressed. The undifferentiated cancers usually occurred in the medial part of the stomach, and most of them were depressed. The differentiated types were localized and they tended to invade the serosa; the undifferentiated types tended to invade the mucosa. Ulcers occurred in 38 differentiated cancer patients and 55 undifferentiated cancer patients; the latter showed a higher susceptibility to ulceration, which was considered to be a secondary pathological condition. Examination of the epithelial changes in the surrounding nonmalignant intestinal mucosa of 95 patients with gastric cancer of the mucosal layer (<4 cm deep) confirmed Nakamura's concept that differentiated cancer follows epidermal transformation of the intestinal mucosa and undifferentiated cancer originates from the gastric mucosa. (15 refs)

- 79-5379 Ten-Year Relative Survival Rate for Stomach Cancer: Comparison of Stomach Cancer Discovered by Mass Screening or in Outpatient Clinics. (Jpn) Sugahara, N. (Cancer Detection Center, Miyagi Cancer Society, Miyagi Prefecture, Japan); Hisamichi, S.; Masuda, Y.; Yanbe, T.; Sakuma, A. *Gan No Rinsho* 25(6): 577-582; 1979.

The postoperative 10-yr survival rates of 391 patients whose stomach cancer was discovered by mass screening (S) and 176 patients whose stomach cancer was discovered in an outpatient clinic (O) were compared. Early stage cancers were found in 82 S and 34 O patients, advanced stage cancers in 270 S and 114 O patients. The 10-yr relative survival rates (actual survival rate/expected survival rate) was 47.4% for S and 33.1% for O. A correlation between the depth of tumor infiltration and relative survival rate showed that there were no significant differences between groups S and O at tumor depths reaching the mucosa, submucosa, muscle layers, or subserosa. There was a marked difference in 10-yr survival rates between the groups when the tumors invaded the serosa (S 30%, O 10.7%). The prognosis of S patients was significantly better ($p < 0.05$) than the prognosis of O patients. (21 refs)

- 79-5380 Primary Occult Tumor of the Ovary. (Jpn) Moriwaki, S. (Dept. Pathology, Matsuyama Natl. Hosp., Matsuyama, Japan); Takashima, S.; Kitajima, T.; Kojima, Y.; Chiba, T.; Kubo, T.; Hayashi, S. *Gan No Rinsho* 25(6): 598-604; 1979.

The frequency and histogenesis of occult ovarian tumors were determined among 3,348 ovaries obtained by surgery for nonovarian disease (carcinoma of the uterine cervix and

EPIDEMIOLOGY AND BIOMETRY

corpus, uterine leiomyoma, oophorectomized breast cancer) or at autopsy from 1,982 patients over the past 11 yr. Benign cystic lesions, including 18 dermoid cysts, were seen in 296/3,348 ovaries. The benign solid tumors that were found included 32 fibromas and/or fibromyomas, 43 Brenner tumors, 2 theca cell tumors, 2 cavernous hemangiomas, and 1 struma ovarii associated with a dermoid cyst. Only one intermediate-type tumor, a granulosa cell tumor, was found. No occult malignant neoplasms were found except for 60 metastatic ovarian tumors; 50 of these tumors were found at autopsy. (14 refs)

- 79-5381 Clinical Statistics on Outpatients During the First Year of Operation of the Hamamatsu University Urology Clinic. (Jpn) Aso, Y. (Dept. Urology, Faculty Medicine, Hamamatsu Univ., Hamamatsu, Japan); Fujita, K.; Tajima, A.; Suzuki, K.; Omi, Y.; Ohta, N. *Acta Urol Jpn* 25(4): 375-378; 1979.

The first-year statistics on outpatients treated at a Japanese urology clinic are reported. Of the 661 patients (455 men, 206 women) treated, 37 (33 men, 4 women) had malignant neoplasms. These included tumors of the bladder (16), prostate (10), testis (4), kidney (3), and renal pelvis, penis, urethra, and retroperitoneum (1 each). (no refs)

- 79-5382 Neoplastic Tumors of the Ovary in Young Women. (Spa) Garcia-Calderon, S. (Facultad de Medicina, Universidad de Barcelona, Barcelona, Spain); Marquez Ramirez, M.; Balasch, J.; Iglesias Guiu, J. *Acta Ginecol (Madr)* 34(1): 25-38; 1979.

During a 7.5-yr period, 92 ovarian tumors were found in 86 women aged <30 yr. Eleven patients (with 11 tumors) were aged 14-19 yr (Group 1), 39 patients (with 42 tumors) were aged 20-24 yr (Group 2); and 36 patients (with 39 tumors) were aged 25-29 yr (Group 3). Potentially malignant borderline tumors were found in 1/11 cases in Group 1, 3/42 cases in Group 2, and 2/39 cases in Group 3. Malignant tumors were found in 4/42 cases in Group 2. The tumors included 22 serous and/or papillary cystadenomas, 2 adenofibromas, 2 serous papillary borderline cystadenomas, 9 mucinous cystadenomas, 4 borderline mucinous cystadenomas, 1 mucinous cystadenocarcinoma, 18 endometrial cysts, 27 benign cystic teratomas, 1 struma ovarii, 3 dysgerminomas, and 2 thecomas. (14 refs)

- 79-5383 Epidemiological Study of Endometrial Carcinoma. (Ita) Rendina, G. M. (I Divisione di Ostetricia e Ginecologia, Ospedale San Camillo De Lellis, Rome, Italy). *Riv Ital Ginecol* 58(3): 153-173; 1979.

The results of a retrospective epidemiological study of 912 cases of endometrial carcinoma diagnosed during 1960-1977 and 100 healthy control women are presented in connection with the recent observation of accompanying endocrinopathy with prevalent dysmetabolic manifestations in patients with endometrial carcinoma. The incidence of obesity was 574/912 vs 41/100; that of the combination of obesity, arterial hypertension, and diabetes, 122/912 vs 4/100. Estrogen therapy was given at one time or another in 663 carcinoma cases, vs 66 controls, with a duration of >3 yr in 491 and 26 cases, respectively. One hundred and four patients and 49 controls received estrogen therapy without estrone; the other patients received conjugated estrogens containing estrone or estrone alone, as compared to 17 controls. The risk factors calculated are 2.5 for obesity; 3 for the combination of obesity, arterial hypertension, and diabetes; 1.37 for estrogen treatment in general; 4.4 for long-term estrogen treatment; and 15.4 for estrone treatment. (38 refs)

- 79-5384 Analysis of Anamnestic Data of Patients with Acute Leukemia. (Pol) Osechin'skii, I. V. (Dept. Epidemiology and Histopathology Leukemia, Central Inst. Hematology and Blood Transfusion, A-167, Novozhikovskii pr. 4, Moscow, USSR); Iashanova, N. D.; Serdobol'ski, V. I.; Kuropteva, I. S. *Acta Haematol Pol* 10(1): 23-30; 1979.

The computerized analysis of qualitative and quantitative anamnestic data concerning 200 children with acute leukemia (108 boys and 92 girls) and 217 healthy children (controls) is presented. The data included information on chronic diseases of the parents, toxemia during pregnancy, number of pregnancies, infectious childhood diseases, allergic reactions, asphyxiation, complications of childbirth, malformations, wt and height at birth, and development. As a result of the computer analysis, 181/200 patients and 204/217 controls were classified correctly. The mean error of the classification was 7.75%. (7 refs)

- 79-5385 Radiation Risk in X-Ray Diagnosis in the Gastrointestinal Tract? (Ger) Vogel, H. (Abteilung Röntgendiagnostik, Universitätsklinik Hamburg, Martinistr. 52, 2000 Hamburg 20, W. Germany). *Roentgenblaetter* 32(6): 314-318; 1979.

The somatic and genetic risks of diagnostic x-ray examinations of the gastrointestinal tract were calculated. The somatic risk, expressed as the number of fatal malignancies or leukemias due to the diagnostic procedure per number of examinations, was found to be highest for angiography (1/25,000), but only 1/300,000-800,000 for diagnostic examinations of the stomach, duodenum, small intestine and colon and for endoscopic retrograde cholangiopancreatography. The genetic risk (risk of malformations) in

the children and grandchildren was highest in the offspring of women subjected to angiography (1/2,300) and of men subjected to radiographic examination of the colon (1/4,300). The genetic risk was generally higher in the offspring of female patients (1/2,300-72,000) than of male patients (1/4,300-280,000). (30 refs)

- 79-5386 Mortality and Morbidity During 13.5 Years' Follow-up in Relation to Blood Pressure. (Eng) Svardsudd, K. (Section Preventive Cardiology, Dept. Medicine I, Sahlgrenska Sjukhuset, Goteborg, Sweden); Tibblin, G. *Acta Med Scand* 205(6): 483-492; 1979.

A study of 855 men born in 1913 revealed a strong association between blood pressure and mortality, regardless of the cause of death. The mortality rate from cancer tended to increase with increasing systolic blood pressure, but the relationship was not consistent in the group with the highest systolic pressure (≥ 175 mm Hg), and it was not significant. There was a significant correlation between diastolic pressure and mortality from cancer ($p \leq 0.05$). (51 refs)

- 79-5387 Applied Diagnostic Techniques: A Decisive Factor in the Long-Term T-Year Survival Rate in Prostatic Carcinoma. (Eng) Trasti, H. (Dept. Urology, Sahlgrenska Sjukhuset, Goteborg, Sweden); Nilsson, S.; Peterson, L. E. *Br J Urol* 51(2): 135-139; 1979.

Data from the Swedish Cancer Registry were used to calculate the incidence, age-adjusted incidence, mortality, and age-adjusted mortality for prostatic carcinoma diagnosed between 1958 and 1971. The correlation coefficient between the proportion of patients diagnosed by cytology only and the age-adjusted incidence was highly significant ($p < 0.001$). The long-term T-year survival rate reflects a complex interplay of multiple factors, including diagnostic technology and techniques for staging and grading. The increase in the reported incidence of prostatic carcinoma in Sweden during this period is discussed in terms of the changes in methods of treatment, diagnosis, and analysis of epidemiological data. (13 refs)

- 79-5388 Tumors of Testis in Jamaica. (Eng) Rao, A. B. (Dept. Surgery, Univ. West Indies, Kingston 7, Jamaica); Sparke, B. *Br J Urol* 51(2): 151-153; 1979.

The incidence of testicular tumors in Jamaica from June 1958 to June 1977 was studied. There were 26 reported

cases, giving a world standardized incidence of 0.40/100,000/yr. Ten patients were aged 30-50 yr and 7 were > 60 yr. In all but one patient, the presenting symptom was swelling of the testis. Two-thirds of the patients had regional node involvement or distant metastases at the time of presentation. The tumors examined histologically included 13 seminomas, 5 embryonic carcinomas, 1 teratoma, 1 Leydig cell tumor, and 1 lymphosarcoma. The Jamaican tumor incidence was higher than that of African blacks but lower than that of North American blacks. The peak age incidence was a decade later than that commonly seen in high-incidence countries. (12 refs)

- 79-5389 Smoking Habits of Bladder Cancer Patients: An Attempt to Quantify Tar Exposition. (Ger) Vutuc, C. (Hygiene-Institut, Universitat Wien, Kinderspitalgasse 15, A-1095 Vienna, Austria); Kunze, M. *Aktuel Urol* 10(3): 159-162; 1979.

The smoking habits of 150 men with cancer of the urinary bladder were studied. One hundred and thirty patients (av age 68.7 yr) were cigarette smokers (the av length of smoking was 42.7 yr), 1 was a pipe smoker, and 19 were nonsmokers. In the general population, the percentage of smokers and former smokers among men aged > 50 yr is 74.5%, ie, significantly lower. Among the cancer patients, 98% of the smokers smoked nonfilter cigarettes with a high tar content (> 25 mg) most of the time or exclusively (47%). In 52% of the cases, the last brand smoked was in this category. Of all brands smoked, the high-tar brands were smoked longest (av 37.4 yr). None of the smokers tended to prefer brands with the lowest tar content (< 15 mg). Although sales of high-tar cigarette brands have decreased in Austria during the last several years, this trend was not applicable to the bladder cancer patients. The findings indicate that the risk of bladder cancer can be reduced substantially by reducing the tar exposure of the smokers, ie, by banning high-tar cigarette brands. (11 refs)

- 79-5390 Metastases in Dermatological Patients with Squamous Cell Carcinoma. (Eng) Moller, R. (Dept. Dermatology, Finsen Inst., 49 Strandboulevard, DK-2100 Copenhagen, Denmark); Reymann, F.; Hou-Jensen, K. *Arch Dermatol* 115(6): 703-705; 1979.

A follow-up study of 211 Danish patients with histologically confirmed squamous cell carcinoma (SCC) diagnosed between 1950 and 1959 was performed. There were 141 men of average age 65.5 yr and 70 women of average age

65.3 yr. Metastases were found in nine men (6.3%) and two women (2.8%). Of the tumors localized to sun-exposed skin, 10/188 metastasized; and 6/55 lip tumors metastasized. All patients with metastases had died, most within 2 yr of diagnosis, eight of them directly from the SCC with metastases. No metastases were found in 40 patients in whom the initial diagnosis of SCC was not confirmed by histologic review. These results and the literature data indicate that three groups of SCC (mucocutaneous, primary cutaneous, and cutaneous secondary to inflammatory and degenerative processes) should be distinguished according to respective incidence of metastases (11%, 3%, and 10%-30%). Skin SCC should be considered a malignant tumor with a higher incidence of metastases than previously assumed. (17 refs)

See also:

- *(Rev.) 79-4803, 79-4809, 79-4811, 79-4812, 79-4813,
79-4815, 79-4817, 79-4824, 79-4827, 79-4830,
79-4833, 79-4843, 79-4854, 79-4857, 79-4882,
79-4898, 79-4906, 79-4918, 79-4919, 79-4920,
79-4921, 79-4922, 79-4923, 79-4924, 79-4925,
79-4926, 79-4927, 79-4928, 79-4929, 79-4930,
79-4931, 79-4932, 79-4933, 79-4937, 79-4938,
79-4939.
- *(Chem.): 79-4948, 79-4972, 49-4973, 79-5019, 79-5020,
79-5032, 79-5055, 79-5056, 79-5090.
- *(Phys.): 79-5098.
- *(Viral): 79-5186.
- *(Immun.): 79-5250.
- *(Path.): 79-5301.

MISCELLANEOUS

- 79-5391 Teratocarcinoma Cells as Vehicles for Introducing Mutant Genes into Mice. (Eng) Mintz, B. (Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111). *Differentiation* 13(1): 25-27; 1979.

The possibility of using cultured teratocarcinoma cells as vehicles for introducing specific mutant genes into mice is discussed. Some of the chief methods by which this may be accomplished are summarized. Of particular interest is the feasibility of constructing mouse models of human genetic diseases. The introduction of markers such as hypoxanthine phosphoribosyltransferase deficiency or chloramphenicol resistance into teratocarcinoma cells are examples of selective schemes upon which experimental production of teratocarcinoma mutant cells can be based. (12 refs)

- 79-5392 5'-Nucleotidase Levels in Permanent Human Lymphoid Cell Lines and Its Implications for Cell Proliferation (Meeting Abstract). (Eng) Sun, A. S. (Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, New York, NY); Holland, J. F.; Slankard-Chahinian, M.; Ohnuma, T. *Clin Res* 26(4): 633A; 1978 (1 ref)

- 79-5393 Metabolism of S-Adenosylhomocysteine and S-Tubercidinylhomocysteine in Neuroblastoma Cells. (Eng) Crooks, P. A. (Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT 06510); Dreyer, R. N.; Coward, J. K. *Biochemistry* 18(12): 2601-2609; 1979.

The metabolism of the methylase product inhibitor S-adenosylhomocysteine (SAH) and its 7-deaza analog S-tubercidinylhomocysteine was studied in cultured N-18 neuroblastoma cells. The latter compound, designed to resist metabolic degradation, was inert under conditions in which SAH was rapidly and extensively degraded. Analyses of the products by high-performance liquid chromatography indicated that the primary route of [¹⁴C]SAH metabolism in the cells leads to adenosine. This product did not accumulate; it was rapidly converted to nucleosides or oxypurines by the action of adenosine kinase and adenosine deaminase, respectively. The presence of the potent adenosine deaminase inhibitor coformycin led to a pronounced inhibition of oxypurine formation, an increase in nucleotide formation, and a slight accumulation of the primary metabolic products adenosine and adenine. (52 refs)

- 79-5394 Cellular Dynamics of Neuronal Cells. The Organization of CSK in Neuroblastoma cells. (Eng) Isenberg, G. (Max Planck Inst. Psychiatry, Munich, W. Germany). *Protides Biol Fluid Proc Cbllq* 26: 595-598; 1978.

The organization of the cytoskeleton in neuroblastoma cells was studied. In the advancing growth cone of a developing neurite, actin filaments were the only filamentous components, and they showed at least two supramolecular aggregation states: a planar filament meshwork and paracrystalline-like filament bundles corresponding to microspikes. Unidirectional polymerization of actin may constitute the primary force-producing mechanism for the advancement of the growth cone. In response to concanavalin A (Con A), neuroblastoma cells underwent marked morphologic changes involving the retraction of neurites and the induction of broad and extensive lamellar regions around the cell periphery. Vinblastine or colchicine caused gradual disintegration of neurites but had no effect on the formation of lamellae. The membranes formed on the induced lamellar regions lacked receptors to Con A from the onset of lamellar formation. Actin appears to be involved in the traction of surface receptors. In the shafts of mature neurites, filamentous actin was restricted specifically to the region just below the plasma membrane. Microtubules were abundant in the core of total neurites, and they could be followed for 10 μ m; 100-A filaments were absent from the growth cones. (5 refs)

- 79-5395 The Effect of Vitamin A on the Migration and DNA Synthesis of Rat Bladder Tumor Cell Line NBT II In Culture. (Eng) Tchao, R. (Dept. Pathology, Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA 19129); Leighton, J. *Invest Urol* 16(6): 476-482; 1979.

The effect of vitamin A on the migration and DNA synthesis of cultured rat bladder tumor cells (line NBT II) was studied. In the presence of vitamin A (2.5-100 units/ml), the NBT II cells grew as a monolayer with diminished piling up. Keratinization, which normally appeared within stratified cells in postconfluent cultures, was inhibited. A "wounding" technique suitable for quantitative analysis of cell migration was developed for confluent cultures grown on glass coverslips. Vitamin A treatment enhanced the migration of cells from the wound edge. In dense postconfluent monolayer cultures, vitamin A treatment maintained a higher percentage of cells in DNA synthesis

MISCELLANEOUS

than that found in the control cultures, as determined by ^3H -thymidine uptake and autoradiography. In sparse cultures, vitamin A did not stimulate DNA synthesis or increase the mitotic index. This stimulatory effect, limited to dense cultures, may be attributable to vitamin A causing viable cells to be shed into the medium, thereby maintaining the monolayer just at confluence. Thus, vitamin A inhibits squamous cell differentiation, enhances migration, and maintains the culture in the proliferative phase. In a different system of high cell density--NBT II aggregates cultured in a combined matrix of chick plasma clot and collagen-coated sponge--vitamin A also enhanced cell migration. These results may explain, in part, the failure of vitamin A to inhibit the growth of some established tumors completely. (30 refs)

- 79-5396 Pyrimidine Pathway Variants of Cultured Mouse Lymphoma Cells with Altered Levels of Both Orotate Phosphoribosyltransferase and Orotidylate Decarboxylase. (Eng) Levinson, B. B. (Howard Hughes Medical Inst. Lab., Univ. California, San Francisco, San Francisco, CA 94143); Ullman, B.; Martin, D. W. *J Biol Chem* 254(11): 4396-4401; 1979.

The isolation and characterization of stable mouse T-lymphoma (S49) cell variants which have altered levels of both orotate phosphoribosyltransferase and orotidylate decarboxylase are reported. These clones were selected for resistance to either 6-azauridine or 5-fluorouracil, two toxic pyrimidine analogs. The cells of one clone, AU-11, are 10-fold more resistant to 6-azauridine than wild type S49 cells and were shown to possess 4 to 6 times higher levels of both orotate phosphoribosyltransferase and orotidylate decarboxylase. Conversely, the cells of a second clone, FU1-2, are resistant to 5-fluorouracil and show a 50% reduction in the levels of both of these enzymes compared to the wild type enzyme levels. This is the first description of the isolation and characterization of mammalian cell variants or mutants with altered activities of the enzymes in the second half of the pyrimidine pathway. The structural and regulatory properties of orotate phosphoribosyltransferase and orotidylate decarboxylase from these clones have been examined. The affinities of orotate phosphoribosyltransferase and orotidylate decarboxylase for autologous substrates, as well as their heat stabilities, isoelectric points, and feedback inhibition by nucleotides are unaltered in these cell types. In addition, the rate of *de novo* pyrimidine biosynthesis, the activity of the glutamine-dependent carbamyl phosphate synthetase, and steady state levels of uridine triphosphate and cytidine triphosphate are essentially unchanged in the variant cells. These presumed mutants provide useful tools for the understanding of the control mechanisms involved in pyrimidine biosynthesis. (43 refs)

- 79-5397 The Effect of Long-Term Food Restriction on Tumours in Rodents. (Eng) Tucker, M. J. (Imperial Chemical Industries Ltd., Pharmaceuticals Div., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England). *Int J Cancer* 23(6): 803-807; 1979.

The effects of relatively small reductions in food intake (approx 20%) on the spontaneous tumor incidence in closed colonies of specific-pathogen-free (SPF) Alderley Park strain I rats and SPF Alderley Park strain I Swiss mice were studied. Dietary restriction (DR) significantly retarded mortality in the mice but not in the rats. Fibrous tumors of the skin in male rats and pituitary and mammary adenomas in the female rats were significantly reduced by DR, as were hepatomas in the male mice and pituitary adenomas in the female mice. Tumors of the Harderian gland, testes, and thymus in the mice and, possibly, brain tumors in the rat appeared to be unaffected by DR, which suggests that they may have a different, perhaps viral, etiology. (22 refs)

- 79-5398 Culture of Normal and Malignant Keratinocytes on Dermal Lamina Densa (Meeting Abstract). (Eng) Regnier, M. (Fondation A. de Rothschild, 29, rue Manin, Paris, France); Prunieras, M. *J Invest Dermatol* 72(5): 284; 1979 (no refs)

- 79-5399 Lipid Composition of Human Malignant Melanoma Tumors at Various Levels of Malignant Growth. (Eng) Portoukalian, J. (Laboratoire de Physiologie Generale et Comparee, Universite Claude-Bernard, 43 Boulevard du 22 Novembre 1918, F-69621 Villeurbanne, France); Zwingelstein, G.; Dore, J. F. *Eur J Biochem* 94(1): 19-23; 1979.

The lipid pattern of 13 human melanomas from various tissues was investigated. Differences in lipid composition were mainly due to neutral lipid levels, particularly the triacylglycerol fraction, which varied from 88% of the total lipids in one tumor to trace amounts in another. However, the fatty acid pattern of this fraction was not significantly different among the tumors, with palmitic and oleic acids being the major components. In the seven tumor samples in which the percentage of malignant melanocytes relative to the total cell population was known, there was a reverse correlation between the proportion of malignant cells and their neutral lipid level. The cholesterol and phospholipid levels were constant among the tumors investigated, as was the molar ratio of cholesterol to phospholipid. The ganglioside pattern was similar in all samples, and GM₃, GM₂, and GD₃ were the major components. There was no correlation between tumor stage and ganglioside pattern. (24 refs)

79-5400 Neoplastic and Nonneoplastic Lesions in Aging F344 Rats. (Eng) Goodman, D. G. (Clement Associates, Inc., 1010 Wisconsin Ave., NW, Washington, DC 20007); Ward, J. M.; Squire, R. A.; Chu, K. C.; Linhart, M. S. *Toxicol Appl Pharmacol* 48(2): 237-248; 1979.

Neoplastic and nonneoplastic lesions in untreated F344 rats used as controls in carcinogenesis tests sponsored by the National Cancer Institute's Carcinogenesis Testing Program over the last 6 yr were tabulated and evaluated. The most common neoplasms in 1,794 male rats were testicular

interstitial cell tumors, leukemias, pituitary adenomas, and adrenal pheochromocytomas. In 1,754 female rats, common tumors were pituitary adenomas, mammary fibroadenomas, uterine endometrial stromal polyps, and leukemias. A variety of less common and rare tumors were seen in almost every tissue. A few malignant neoplasms were metastatic. Nonneoplastic lesions included nephropathy, cardiomyopathy, focal hyperplasias in a variety of tissues, and inflammatory lesions of the uterus. The focal hyperplasias were suggestive of the early stages of neoplasia in the lung, liver, pituitary, adrenal, thyroid, and testis. (17 refs)

Author Index

- Aaronson, S. A., 79-5151
 Abakumova, O. Iu., 79-5057
 Abe, S., 79-5317
 Abe, T., 79-5096
 Adams, A., 79-4893
 Adams, C., 79-5108
 Ahmed, M., 79-5076
 Ahokas, J. T., 79-5062
 Aizawa, Y., 79-5272
 Albert, D. M., 79-5148
 Albert, E., 79-5306
 Alexander, P., 79-5270
 Alfred, L. J., 79-5100
 Allen, C. E., 79-4975
 Alsabti, E. A., 79-5252
 Althoff, J., 79-4991, 79-5017
 79-5018
 Althouse, R., 79-4817
 Alvarez-Berdecia, A., 79-5312
 Anderson, J., 79-5040
 Anderson, K. P., 79-5177
 Anderson, L. C., 79-5164
 Anderson, R. L., 79-4983
 Andersson-Anvret, M., 79-4893
 Andrese, A. P., 79-5167
 Andrews, A. W., 79-4984
 Anselme, J. P., 79-4820
 Antos, M., 79-5278
 Aoki, Y., 79-5011
 Appel, K. E., 79-4990
 Arakawa, M., 79-5378
 Arendes, J., 79-5176
 Arffmann, E., 79-5052
 Argyris, T. S., 79-4910
 Arkhipov, G. N., 79-4824
 Arlin, M., 79-4926
 Arrhenius, E., 79-4958
 Artamonova, V., 79-5206
 Arvin, A. M., 79-5159
 Asahina, S., 79-5019
 Ashman, R. B., 79-4877
 Aso, Y., 79-5381
 Athan, E., 79-5138
 Atikkan, E. E., 79-4966
 Atta, G. J., 79-5049
 Audet-Lapointe, P., 79-5351
 Audigier, J. C., 79-5373
 Auerbach, O., 79-4845
 August, J. T., 79-5141
 Aune, T., 79-5022
 Austin, G. E., 79-4986
 Avery, R. J., 79-5128
 Avidor, I., 79-5083
 Avila, R., 79-5367
 Aya, T., 79-5163
 Bacci, M., 79-5340
 Bach, F. H., 79-5249
 Bachelier, L. T., 79-5133
 Bader, M., 79-5359
 Bahna, L., 79-5069
 Baillot, R., 79-5305
 Baker, M. A., 79-5042
 Bal, E., 79-5241
 Balasch, J., 79-5382
 Balducci, L., 79-5318
 Baldwin, R. W., 79-4907, 79-5054
 Bandele, S. D., 79-4865
 Bandu, M. T., 79-5173
 Banerjee, M. R., 79-4972
 Bannasch, P., 79-4981
 Barbieri-Weill, D., 79-5138
 Barnes, R. M., 79-5235
 Barrick, J., 79-5286
 Bartholomew, L. G., 79-5303
 Barton, R., 79-4821
 Basilico, C., 79-5216
 Bates, D. V., 79-4812
 Bates, R. C., 79-5155
 Baucom, K., 79-5084
 Bauer, F. L., 79-4955
 Baumgartner, A. P., 79-5079
 Bayer, U., 79-5009
 Bayless, T. M., 79-5309
 Baylin, S. B., 79-5309
 Beamand, J. A., 79-5117
 Beaumatin, J., 79-5025
 Beck, D. W., 79-5315
 Becker, Y., 79-4868
 Beckman, E. M., 79-5354
 Beebe, G. W., 79-4858
 Begemann, H., 79-5250
 Bellanti, J. A., 79-5175
 Ben-Bassat, H., 79-4905
 Bender, J., 79-5302
 Benedict, W. F., 79-5100
 Benjamin, T., 79-5207
 Benner, R., 79-5245
 Benteleva, T. A., 79-5253
 Berenblum, I., 79-4803
 Berg, P., 79-5212, 79-5214, 79-5215
 Bergers, A. M., 79-5222
 Berghaus, I., 79-5254
 Berlatzky, Y., 79-5114
 Bernfeld, P., 79-4845
 Berridge, M. V., 79-5259
 Beurlet, J., 79-5086
 Bevan, D. R., 79-4810
 Beyer, H. K., 79-5242
 Bidlingmaier, F., 79-5306
 Bismuth, H., 79-5034
 Bjeldanes, L. F., 79-5028
 Bjursell, G., 79-5203
 Black, P. H., 79-5209
 Blade, L., 79-5364
 Blair, D. G., 79-5134
 Blattner, W. A., 79-5290, 79-5295
 Blumberg, W. E., 79-4811, 79-4843
 Bocharov, A. F., 79-5196
 Boll, W., 79-5208
 Bolognesi, C., 79-4999
 Bolt, H. M., 79-4962
 Bompiani, A., 79-5087
 Bonenfant, J. L., 79-5327
 Bootman, J., 79-4964
 Bornkamm, G. W., 79-4889
 Bouillant, A., 79-5327
 Bourke, J. B., 79-5372
 Boutibonnes, P., 79-5029
 Bouveng, R., 79-5046
 Bowers, E. J., 79-4819
 Boyd, A. L., 79-4880
 Boyland, E., 79-4920
 Brambilla, G., 79-4999
 Brandeis, W. E., 79-5240
 Braun, D. P., 79-5234
 Breinig, M. C., 79-5194
 Breistein, L. S., 79-5075
 Brennan, M. F., 79-5324
 Broker, T. R., 79-5202
 Brookes, P., 79-5085
 Brown, C. A., 79-5049
 Brown, J. P., 79-5263
 Brown, S. M., 79-5179, 79-5186
 Brozovich, B. J., 79-4952
 Bruce, D. A., 79-5312
 Bruland, K. W., 79-5098
 Bryan, G. T., 79-4846
 Bryant, D. W., 79-5000
 Brychcy, T., 79-4953
 Burger, M. M., 79-5323
 Burke, D. C., 79-5129
 Burn, J. L., 79-5266
 Burnett, K. R., 79-5006
 Burt, M. E., 79-5324
 Busch, F. W., 79-5014
 Buser, H. R., 79-5094
 Busey, W. M., 79-4976
 Busta, F. F., 79-4975
 Bynum, G. D., 79-4941
 Cadotte, M., 79-5292
 Caine, M., 79-5114
 Cairns, J., 79-4936
 Calarco, P. G., 79-5223
 Calne, R. Y., 79-4904
 Cameron, J. L., 79-5309
 Capel, I. D., 79-4956
 Cappellotto, P., 79-5314
 Carbone, A., 79-4901
 Carey, T. E., 79-5276
 Carlborg, F. W., 79-4923
 Carlo, P., 79-4999
 Carne, T., 79-5021
 Carr, B. I., 79-5249
 Carrel, S., 79-5243
 Carroll, A. R., 79-5230
 Cartwright, R. A., 79-5283
 Cashdollar, L. W., 79-5205
 Cassell, P. G., 79-5040
 Cathcart, M. K., 79-5219
 Catt, D. L., 79-5106
 Cauchy, L., 79-5122
 Cavaliere, A., 79-5340
 Cavanna, M., 79-4999
 Celis, E., 79-5251
 Center, M., 79-4888
 Cernosek, S. F., 79-5081
 Chaigneau, M., 79-4957
 Challand, B. J., 79-5239
 Chan, T. H., 79-4968
 Chandradasa, K. D., 79-5235, 79-5274
 Chandrasekhar, A. J., 79-5108
 Chang, C. C., 79-4909

- Chang, C. F., 79-5033
 Chang, R. L., 79-5060
 Chang, T. W., 79-5251
 Chapman, P. H., 79-5277
 Charbonneau, A., 79-5351
 Charbonnet, L., 79-5126
 Chasseaud, L. F., 79-4841
 Chatterjee, S., 79-5157
 Chen, M. S., 79-5180
 Cheng, Y. C., 79-5191
 Cherry, M., 79-5237
 Chian, E. S., 79-4837
 Chiba, T., 79-5380
 Chipman, J. K., 79-5068
 Chlud, K., 79-4834
 Chodynicky, S., 79-5365
 Choppin, P. W., 79-5229
 Chow, L. T., 79-5202
 Chrisman, C. L., 79-5079
 Christodoulides, L., 79-4985
 Chu, K. C., 79-5400
 Clark, M. A., 79-5299
 Clausen, O. P., 79-4973
 Clawson, A. J., 79-5031
 Cleary, B. K., 79-5336
 Clelland, R. C., 79-4819
 Coakley, D. V., 79-5370
 Coate, W. B., 79-4960
 Cocito, C. G., 79-5273
 Coetzee, S., 79-5153
 Cohen, J. R., 79-5293
 Cohen, S. M., 79-4864, 79-4993
 Cole, C., 79-5212
 Cole, C. N., 79-5215
 Coleman, M. B., 79-5318
 Colyer, S. P., 79-5101
 Con-Wong, R., 79-5001
 Conan, L., 79-4957
 Conlan, A. A., 79-5328
 Conner, B., 79-4886
 Conney, A. H., 79-5060
 Connor, T. H., 79-4816
 Consigli, R. A., 79-4888
 Coppeto, J. R., 79-5102
 Cortini, R., 79-5188
 Costlow, M. E., 79-5047
 Coudert, F., 79-5122
 Coutelle, R., 79-5071
 Coward, J. K., 79-5393
 Cowie, A., 79-5204
 Cox, R. H., 79-5003
 Craig, D. K., 79-5106
 Crawford, L. V., 79-5214, 79-5215
 Crawford, M. A., 79-5175
 Crawley, A., 79-4979
 Creger, W. P., 79-5293
 Crittenden, L. B., 79-5118
 Croce, C. M., 79-5286
 Croissant, O., 79-5172
 Crooks, P. A., 79-5393
 Cuatrecasas, P., 79-4818
 Cunningham-Rundles, C., 79-5240
 Currie, G. A., 79-5270
 Curtis, G., 79-5256
 Cutter, G. A., 79-5098
 Dal Canto, M. C., 79-5232
 Dalquen, P., 79-5017
 Dambrine, G., 79-5122
 Daniels, C. A., 79-5195
 Dansette, P. M., 79-5060
 Darai, G., 79-5192
 Davey, G. C., 79-5270
 David, A., 79-5375
 Davies, J. S., 79-5330
 Davisson, P. B., 79-5144
 Day, N. K., 79-5240
 Day, R. S., 79-5200
 Daynes, R. A., 79-5099
 de Alleluia, I. B., 79-4857
 de Arcos de la Plaza, M., 79-4933
 De Boer, J., 79-5111
 de Campos, M., 79-5032
 de Heer, K., 79-4977
 de la Pena, N. C., 79-5241
 de Lignieres, B., 79-4851
 De Loecker, W., 79-5070
 De Lustig, E. S., 79-5241
 de Serres, F. J., 79-4804
 de The, G., 79-4882, 79-5166
 De Villiers, E. M., 79-5153
 de Vries, A. A., 79-5301
 De Wever, F., 79-5070
 Dean, J. H., 79-5290
 Decoufle, P., 79-5361
 Deinhardt, F., 79-4879, 79-4883
 Dement, J. M., 79-5363
 Dempsey, A. N., 79-5371
 Denda, A., 79-5011
 DerHagopian, R. P., 79-5287
 Desgranges, C., 79-5166
 Devasagayam, T. P., 79-4969
 deVeber, G. A., 79-5042
 Devlin, M., 79-5186
 DeWalle, F. B., 79-4837
 Deyhle, P., 79-5377
 Diad'kova, A. M., 79-5224
 Diaz, A., 79-5241
 Diefenthal, W., 79-5185
 Diggelmann, H., 79-5116
 Dille, B. J., 79-5232
 Dilworth, P., 79-5016
 Dimpfl, J., 79-5231
 DiRaddo, P., 79-4968
 Dobos, M., 79-4994
 Doerfler, W., 79-5198
 Dohrmann, J., 79-5250
 Doi, H., 79-5335
 Doms, D., 79-5070
 Donahoe, J. P., 79-5125
 Dore, J. F., 79-5399
 Dorrel, H. M., 79-4956
 Dostal, V., 79-5187
 Dowler, J. B., 79-5371
 Drake, C. G., 79-5315
 Drake, J., 79-4801
 Drath, D. B., 79-5015
 Dray, S., 79-5234
 Drevon, C., 79-4959
 Dreyer, R. N., 79-5393
 du Vivier, A. W., 79-4861
 DuFrain, R. J., 79-5101
 Dulbecco, R., 79-4866
 Dumas, L., 79-5327
 Duncan, S. J., 79-5085
 Dusek, Z., 79-5069
 Dybing, E., 79-5022
 Dziewulska-Bokinić, A., 79-5103
 Eapen, J., 79-4969
 Easty, G. C., 79-5280
 Ebdon, D. S., 79-5372
 Edidin, M., 79-5262
 Edwards, A., 79-5275
 Egan, B., 79-5364
 Eidson, C. S., 79-5125
 Eimermacher, H., 79-5242
 Eisen, H. N., 79-5251
 Eisinger, J., 79-4811
 Elkins, W. L., 79-5244
 Ellerton, J. A., 79-5042
 Ellman, M., 79-5046
 Elson, C. J., 79-5274
 Emanoil-Ravcovitch, R., 79-5138
 Embleton, M. J., 79-5054
 Enaka, K., 79-5026
 Enderby, G., 79-5021
 Engelhardt, D. L., 79-5178
 Enke, H., 79-5071
 Epstein, M. A., 79-5168
 Epstein, S. S., 79-5019
 Essex, M., 79-5152
 Evans, A. S., 79-4874
 Evans, D. I., 79-5266
 Evans, D. M., 79-5336
 Evans, J. L., 79-5082
 Eylan, E., 79-5136
 Fabisch, P., 79-5146
 Falck, K., 79-5090
 Falcone, M. W., 79-5320
 Falk, L., 79-4893
 Falke, D., 79-5176
 Famulari, N. G., 79-5145
 Fan, H., 79-5133
 Farago, G. A., 79-5016
 Farrelly, J. G., 79-4997
 Favaloro, J., 79-5204
 Favre, M., 79-5172
 Feild, J., 79-5131
 Feind, C. R., 79-5300
 Feinstein, A. R., 79-4932
 Fekete, G., 79-4994
 Fenner, F., 79-4897
 Fenoglio, C. M., 79-5193
 Fernandez-Rojo, F., 79-5346
 Ferris, F., 79-4922
 Feunteun, J., 79-5214
 Fiers, W., 79-5212, 79-5214
 Filser, J. G., 79-4962
 Finch, E. A., 79-5134
 Fine, D. H., 79-5010
 Finerty, S., 79-5168
 Finollo, R., 79-4999
 Fiore, D., 79-5314
 Fishman, P. H., 79-4966
 Fishman, R. S., 79-5303
 Flammang, T., 79-5021
 Flavell, A. J., 79-5204
 Flesher, J. W., 79-5065
 Fohring, B., 79-5201
 Fong, C. K., 79-5149
 Forni, G., 79-5246
 Forsberg, J. G., 79-5075

Foster, S. J., 79-5072
 Fouassin, A., 79-5066
 Foucault, B., 79-4957
 Fowler, A. K., 79-5137
 Fox, H., 79-4855
 Fox, R. R., 79-5237
 Franco, D., 79-5034
 Frankel, A. E., 79-5151
 Franklin, J. A., 79-5119
 Franklin, R. B., 79-5120
 Franklin, S., 79-5308
 Fraumeni, J. F., 79-5290, 79-5295
 79-5356
 Frenkel, L. D., 79-5175
 Frenkel, N., 79-4876
 Fresen, K. O., 79-4889
 Frezza, D., 79-4988
 Friberg, J., 79-4921
 Fribush, H. M., 79-4821
 Fried, M., 79-5208
 Friede, R. L., 79-5316
 Friedell, G. H., 79-4993
 Frith, C. H., 79-5341
 Frockt, I. J., 79-5024
 Froines, J. R., 79-5363
 Fuhrman, J., 79-5265
 Fujii, G., 79-5304
 Fujii, K., 79-5019
 Fujinami, R. S., 79-5228
 Fujita, K., 79-5381
 Fukamachi, H., 79-5002
 Fukuda, Y., 79-5036
 Fуска, M., 79-4951
 Gahmberg, C. G., 79-5164
 Gall, S. A., 79-5195
 Gallager, H. S., 79-5345
 Gallagher, P. E., 79-5047
 Gallatin, W. M., 79-5121
 Gangolli, S. D., 79-4989
 Gans, P. J., 79-5144
 Garcia-Calderon, S., 79-5382
 Garfinkel, L., 79-4845
 Garrido, F., 79-5248
 Garry, R. F., 79-5227
 Gazit, A., 79-5136
 Geis, A., 79-5201
 Gelboin, H. V., 79-4839
 Gelinas, R. E., 79-5202
 Gelpi, A. P., 79-5170
 Genest, P., 79-5327
 Gerdes, H., 79-4847
 Gervin, A. S., 79-5307
 Getaz, E. P., 79-4906
 Giese, A. C., 79-4856
 Giggs, J. A., 79-5372
 Gilbert, J. H., 79-5151
 Gilden, D. H., 79-5186
 Giovarelli, M., 79-5246
 Girard, R. M., 79-5305
 Given, D., 79-5160
 Glaser, R., 79-4886
 Glaser, Z. R., 79-4809
 Glatt, H. R., 79-5078
 Glinkski, W., 79-5172
 Gnewuch, C. T., 79-4823
 Goff, U., 79-5010
 Goh, K., 79-5043

Gol'bert, Z. V., 79-4915
 Gold, E. B., 79-5357
 Goldblum, N., 79-4905
 Goldman, E., 79-5207
 Golovin, D. I., 79-5322
 Good, R. A., 79-5240
 Goodman, D. G., 79-5400
 Goodman, Z. D., 79-5343
 Gopinath, C., 79-5298
 Gordis, L., 79-5357
 Gori, G. B., 79-4930
 Goto, S., 79-5335
 Gouesnard, J. P., 79-4987
 Goulian, M., 79-5132
 Graff, J., 79-5281
 Grandjean, J. P., 79-5086
 Grant, W. F., 79-4832
 Greeder, G., 79-4950
 Greenaway, P., 79-5208
 Greenbaum, E., 79-5006
 Greenberg, P. L., 79-5291, 79-5293
 Greenberger, J. S., 79-5144
 Greene, M. H., 79-5295
 Greenfield, R. S., 79-5217
 Gregerson, D. S., 79-5147, 79-5148
 Greither, A., 79-5321
 Gresser, I., 79-5173
 Griquite, L., 79-4808
 Griem, K., 79-5160
 Grohn, P., 79-5090
 Groppe, C. W., 79-4995
 Gross, N., 79-5243
 Grosse-Wilde, H., 79-5306
 Groth, D. H., 79-5024
 Guardia, J., 79-5331
 Guenther, T. M., 79-5073
 Guerard, M. J., 79-5351
 Gulvas, F. A., 79-5118
 Gunnarsson, P. O., 79-5046
 Gunven, P., 79-5165
 Gustafsson, J. A., 79-4931
 Gutierrez-Cernosek, R. M., 79-5081
 Gutschmidt, E., 79-5269
 Haack, D. G., 79-4845
 Haas, H., 79-5018
 Haberman, H. F., 79-5271
 Habermehl, K. O., 79-5185
 Hagenfeldt, K., 79-4931
 Halpern, J. W., 79-5170
 Hamada, M., 79-5003
 Hamilton, P. B., 79-5033
 Hammond, E. C., 79-4845
 Hampar, B., 79-4880
 Hampl, H., 79-5185
 Hamstra, R. D., 79-5288
 Haneke, E., 79-5269
 Hanna, M. L., 79-4949
 Hansen, J. A., 79-5263
 Happe, J. A., 79-4949
 Harada, W., 79-4845
 Harden, T. K., 79-5072
 Harel, J., 79-5138
 Harris, R. A., 79-4989
 Harrison, L. H., 79-5348
 Hartley-Asp, B., 79-4996
 Hashimoto, Y., 79-4992
 Hastings, O. M., 79-5329

Hata, T., 79-4982
 Hattori, J., 79-5207
 Hay, K. A., 79-5184
 Hayashi, S., 79-5380
 Hazlitt, L. G., 79-4823
 Hecker, L. I., 79-4997
 Hedderson, E. D., 79-5278
 Heddle, J. A., 79-5059
 Heese, B., 79-4813
 Hehir, M. E., 79-4861
 Heilmann, E., 79-5254
 Heinonen, E., 79-5090
 Heitz, P., 79-5017
 Hellman, A., 79-5137
 Hellmann, H., 79-5056
 Hellstrom, I., 79-5263
 Hellstrom, K. E., 79-5263
 Henle, G., 79-4873, 79-4894
 Henle, W., 79-4873, 79-4894
 Henry, R. C., 79-5325
 Herring, D. W., 79-5283
 Hersey, P., 79-5275
 Hersh, E. M., 79-5239
 Heslop, B. F., 79-5259
 Heumann, D., 79-5243
 Hilgard, P., 79-5257
 Hill, M., 79-5115
 Hill, M. J., 79-5040
 Hinuma, Y., 79-5096, 79-5097
 Hirakawa, T., 79-5064
 Hirano, F., 79-5012
 Hirono, I., 79-5035
 Hirota, N., 79-5013
 Hirt, H. M., 79-4911
 Hisamichi, S., 79-5379
 Hjorne, N., 79-5052
 Ho, J. H., 79-5167
 Hoexter, B., 79-5113
 Hoffmann, P. J., 79-5191
 Hollaender, A., 79-4801
 Holland, J. F., 79-5392
 Holland, L. E., 79-5177
 Holsti, L. R., 79-5090
 Homburger, F., 79-5017
 Honeyman, E. M., 79-5275
 Hood, L. E., 79-5265
 Hope, J., 79-4940
 Horwitz, R. I., 79-4932
 Hou-Jensen, K., 79-5390
 Howatson, A. G., 79-5040
 Hradec, J., 79-5069
 Hrubec, Z., 79-5356
 Hsiung, G. D., 79-5149
 Hsu, M. C., 79-5229
 Hsueh, A. J., 79-5080
 Huber, C., 79-5250
 Huber, G. L., 79-5015
 Huff, J. E., 79-4817
 Hughes, J. V., 79-5232
 Huibregtse, K., 79-5111
 Hull, M. A., 79-5134
 Hultmark, D., 79-4958
 Hunt, J., 79-5334
 Hunter, E., 79-5157
 Hunter, T., 79-5199, 79-5211
 Hurwitz, S., 79-5328
 Hussein, M. A., 79-5233

- Hutcheon, D. F., 79-5309
Hutschenreiter, G., 79-5281
Hutt, L. M., 79-5169
Hylden, J. L., 79-4810
Hyman, R. W., 79-4887
Iacobelli, S., 79-5087
Iashanova, N. D., 79-5384
Ichinoe, K., 79-5350
Iglesias Guiu, J., 79-5382
Ii, Y., 79-4991
Ikeda, T., 79-5335
Iltis, J. P., 79-4887
Imamura, A., 79-5037
Infante, P. F., 79-5358
Inglis, A. M., 79-5319
Inoue, S., 79-4951
Inui, N., 79-5304
Inui, S., 79-5011
Iraci, G., 79-5314
Isenberg, G., 79-5394
Isenberg, R. A., 79-5170
Ishikawa, T., 79-5064
Isner, J. M., 79-5320
Isomura, T., 79-5339, 79-5378
Iversen, O. H., 79-5041
Iversen, U. M., 79-5041
Iwamoto, G., 79-5339
Jablonska, S., 79-5172
Jacobi, G., 79-5281
Jacobson, M. K., 79-4821
Jaggi, W., 79-5061
Jain, K. M., 79-5329
Jamieson, A. T., 79-5179
Janerich, D. T., 79-5360
Jarzabek-Chorzelska, M., 79-5172
Jassem, J., 79-5103
Jeannet, M., 79-5247
Jelalian, K., 79-5145
Jenner, M., 79-4956
Jensen, G., 79-5046
Jensen, N. M., 79-4840
Jerina, D. M., 79-5060
Jessen, R. T., 79-4862
Jick, H., 79-4932
Johansson, L., 79-4958
Johnson, F. C., 79-4844
Johnson, H. J., 79-5081
Johnson, T. C., 79-5232
Joiner, E. E., 79-5101
Jonen, H. G., 79-5004
Jones, A. W., 79-5330
Jones, K. W., 79-5193
Jordan, M. C., 79-5158
Joyner, J., 79-5127
Jukes, T. H., 79-4807
Jurek, A., 79-4963
Kadlubar, F., 79-5021
Kahl, G. F., 79-5063
Kahlon, P. S., 79-4972
Kahn, P., 79-5261
Kalmar, L., 79-4994
Kamada, N., 79-5096, 79-5097
Kamen, R., 79-5204
Kanazawa, K., 79-4942, 79-4943
Kanerva, R. L., 79-4983
Kaplan, J. C., 79-5209
Kapp, R. W., 79-4960
Karnik, V., 79-5053
Karnovsky, M. L., 79-5015
Kasahara, Y., 79-5378
Kassell, N. F., 79-5315
Kato, K., 79-5035
Kato, S., 79-5037
Katoh, T., 79-5051
Katsuki, T., 79-5096, 79-5097
Katz, M., 79-5059
Katzanevas, A., 79-4833
Kaufman, D. W., 79-5362
Kaufman, J. J., 79-5308
Kawaguchi, T., 79-5109
Kawai, T., 79-4978, 79-5035
Kawakubo, Y., 79-4982
Kawalek, J. C., 79-4984
Keefer, L. K., 79-4826
Kehry, M., 79-5265
Keller, C., 79-4857
Kelly, J. K., 79-5330
Kennel, S. J., 79-5139
Keown, K., 79-5307
Ketkar, M. B., 79-5018
Ketterer, B., 79-4985, 79-5021
Khan, A. S., 79-5313
Khanduja, K. L., 79-5048
Kieff, E., 79-5160
Kikuchi, Y., 79-5051
Kilbey, B. J., 79-4801
Kilpatrick, B. A., 79-5202
Kim, G., 79-5095
Kimura, N., 79-5326
Kirchner, H., 79-4911, 79-5174
Kirichenko, V. E., 79-5020
Kirkowski, A. C., 79-5082
Kirrane, J., 79-4850
Kishida, T., 79-5255
Kitagawa, H. S., 79-4992
Kitagawa, T., 79-5064
Kitajima, T., 79-5380
Kitamura, H., 79-5109
Kitamura, S., 79-5036
Kitsak, V. Ia., 79-5196
Klaiber, H., 79-5377
Klaus, E., 79-5063
Klein, B., 79-5208
Klein, G., 79-4890, 79-4916, 79-5165
Klement, V., 79-5141
Kleven, S. H., 79-5125
Kligerman, A. D., 79-4998
Klippel, K. F., 79-5281
Kliucharev, B. V., 79-5253
Knapka, J. J., 79-4825
Kniazev, P. G., 79-5224
Knorr, D., 79-5306
Kobayashi, W., 79-5051
Kobler, E., 79-5377
Koch, K. S., 79-4938
Kochen, M., 79-4911
Koda, M., 79-5037
Koeda, T., 79-5012
Koepke, S. R., 79-4822
Kohlmann, H. W., 79-5332
Kojima, Y., 79-5380
Kojiro, M., 79-5339, 79-5378
Komiya, K., 79-4982
Kommineni, C., 79-5024
Komura, T., 79-5378
Konetzke, G., 79-4854
Konishi, Y., 79-5011
Konrad, H. R., 79-5107
Koomey, M., 79-5201
Koprowski, H., 79-5186, 79-5286
Korach, K. S., 79-5084
Korobitsyn, L. P., 79-5224
Korosteleva, T. A., 79-5253
Korosteleva, V. S., 79-5226
Koseki, Y., 79-5047
Kosiakov, P. N., 79-5226
Kosiakova, N. P., 79-5226
Kouri, R. E., 79-5127
Kram, D., 79-4941
Kramer, S. N., 79-5299
Kredich, N. M., 79-5258
Kreyberg, L., 79-5369
Kroeger-Koepke, M. B., 79-4822
Kromarova, B., 79-5376
Krull, I. S., 79-5010
Kruttsch, H., 79-5238
Kubo, T., 79-5380
Kubota, K., 79-5279
Kulakova, A. M., 79-5226
Kulikova, G. S., 79-5020
Kumar, S., 79-5060
Kung, M. P., 79-5191
Kunitake, K., 79-5378
Kunz, W., 79-4990
Kunze, M., 79-5389
Kupper, R. J., 79-4822
Kuramoto, A., 79-5096, 79-5097
Kurebayashi, H., 79-4970
Kuroki, T., 79-4959
Kuropteva, I. S., 79-5384
Kurt, T. L., 79-4845
Kurtz, S. M., 79-5297
Kusunoki, T., 79-5255
Kutsenko, N. G., 79-5057
Kuwabara, N., 79-5036
Kuznetsov, O. K., 79-5224
Kyriakides, G. K., 79-5076
Labow, S. B., 79-5113
Lack, E. E., 79-5299
Ladyga, M., 79-4963
Lagace, R., 79-5327
Lai, S. P., 79-5199
Laib, R. J., 79-4962
Lake, B. G., 79-4989
Lakowicz, J. R., 79-4810
Lakshmi, M. S., 79-5220
Lambert, R., 79-5373
Lancaster, W. D., 79-5156
Land, C. E., 79-4858
Land, E. J., 79-5093
Landolfo, S., 79-5246
Lantos, P. L., 79-4980
Larner, E., 79-5154
Larraga, V., 79-5262
Lauriola, L., 79-4901
Lausch, R. N., 79-5184
Lawrence, C., 79-5199
Lazarev, N. I., 79-4849
Lazaro, E. J., 79-5329
Le Gresley, L. P., 79-5305
Le Moan, G., 79-4957

- Leadbetter, G. W., 79-5112
79-5338
Lee, D., 79-5040
Lee, L. S., 79-5077
Leffert, H. L., 79-4938
Legon, S., 79-5204
Legraverend, C., 79-5063
Lehmann, A. R., 79-5091
Lehmann, E. C., 79-5319
Lehmann, F. G., 79-4847
Lehner, T., 79-5181
Lehr, R. E., 79-5060
Leibovitch, S. A., 79-5138
Leibson, P. J., 79-5264
Leighton, J., 79-5395
Leipolz-Angermuller, S., 79-5110
Lemon, S. M., 79-5169
Lennette, E. T., 79-4894
Lerman, M. I., 79-5057
Levin, W., 79-5060
Levine, P. H., 79-5167
Levinson, B. B., 79-5396
Levy, J. A., 79-5127, 79-5128
79-5231
Levy, L., 79-5084
Levy, S., 79-4967
LeWinn, E. B., 79-4848
Lewis, G. P., 79-4842
Lewis, T. R., 79-4976
Leyman, A. M., 79-5070
Li, F. P., 79-5289, 79-5295
Li, J. L., 79-5169
Light, W. G., 79-4810
Lijinsky, W., 79-4836
Lijovetzky, G., 79-5114
Liljekvist, J., 79-5046
Lindahl, T., 79-4893
Linemeyer, D., 79-5131
Linhart, M. S., 79-5400
Linnenbach, A., 79-5286
Liotta, L. A., 79-5317
Lipsett, M. B., 79-4929
Littlefield, L. G., 79-5101
Livingston, A. E., 79-4952
LiVolsi, V. A., 79-5300
Lloyd, K. O., 79-5276
Lodge, D. C., 79-4964
Loeppky, R. N., 79-4823
Loew, G. H., 79-5038
Loken, M. R., 79-5264
Longenecker, B. M., 79-5121
Lopez, C., 79-5182
Loquet, C., 79-5029
Lu, C., 79-5000
Lucier, G. W., 79-5050
Lukes, R. J., 79-5294
Lutz, W. K., 79-5061
Luzzatto, R., 79-5345
Lyle, G. G., 79-4821
Lyle, R. E., 79-4821
MacGregor, J. T., 79-4908
Mach, J. P., 79-5243
MacKenzie, K. M., 79-5050
Mackey, B. E., 79-4908
Macklin, A. W., 79-4818
MacLeod, I. B., 79-5040
Macnab, J. C., 79-5236
Maddin, W. S., 79-5104
Magnusson, G., 79-5298
Mahmood, T., 79-5288
Maitland, N. J., 79-5193
Majeed, S. K., 79-5298
Mak, T. W., 79-5143
Malek, B., 79-5375, 79-5376
Malone, J. M., 79-5307
Malt, R. A., 79-4955
Manero, S., 79-5346
Mangham, B. A., 79-4842
Mango, G., 79-4901
Manis, J., 79-5095
Manservigi, R., 79-4869
Mara, B., 79-5291
Marchetto, D. J., 79-5289
Mareel, M., 79-5285
Mariage, R., 79-5115
Markovits, P., 79-4967
Marquardt, H., 79-5009
Marquez Ramirez, M., 79-5382
Marsden, H. S., 79-5188
Marten, R. H., 79-4861
Martin, D. W., 79-5396
Martin, G. J., 79-4987
Martin, G. R., 79-5317
Martinez-Merino, A., 79-5346
Maruta, A., 79-5026
Mastromatteo, W. P., 79-5278
Masuda, Y., 79-5379
Matsuo, T., 79-5163
Matter, A., 79-5323
Matter, B., 79-4801
Mattingly, P. C., 79-5333
Matuura, S., 79-5335
Maury, C., 79-5173
Mauvais-Jarvis, P., 79-4851
Mayer, D., 79-4981
Mays, C. W., 79-4859
McCalla, D. R., 79-5000
McCarthy, W. H., 79-5016, 79-5275
McClung, J. E., 79-5171
McCoy, E. C., 79-4954
McCue, R., 79-5126
McDonald, A. D., 79-4852
McDougall, J. K., 79-5193
McDowell, J. W., 79-5272
McGeorge, M. B., 79-5194
McKee, R. H., 79-5005
McKeen, E. A., 79-5295
McKinley, W. A., 79-4823
McLachlan, J. A., 79-5084
McNeillage, L. J., 79-5259
Menard, R. H., 79-5073
Menezes, S., 79-4967
Meng, H., 79-4837
Menon, M. A., 79-5368
Meot, B., 79-5374
Mercier, M., 79-5066
Meredith, P. A., 79-4814
Meredith, R. F., 79-4952
Merigan, T. C., 79-5159
Merwin, C. F., 79-4862
Mestrallet, G., 79-5086
Metzler, M., 79-5078, 79-5084
Meyvisch, C., 79-5285
Michejda, C. J., 79-4822
Michell, R. H., 79-4935
Michot, B., 79-5273
Micolonghi, T. S., 79-5272
Miettinen, O. S., 79-5362
Migone, N., 79-4835
Miles, K., 79-5135
Miller, G., 79-5162
Miller, G. H., 79-4845
Miller, J. B., 79-5006
Miller, J. F., 79-4902
Miller, R., 79-5297
Miller, R. G., 79-5170
Miller, R. W., 79-4815
Milligan, F. D., 79-5343
Milner, J. A., 79-4950
Miltenyi, M., 79-4994
Milton, G. W., 79-5016
Mintz, B., 79-5391
Misoguchi, M., 79-5339
Mitschke, H., 79-4977
Miyake, H., 79-5335
Miyamoto, N., 79-5326
Miyashita, T., 79-5335
Miyoshi, A., 79-5378
Mizell, M., 79-5126
Mizuno, F., 79-5163
Mogilevskii, I. L., 79-5226
Moisan, T., 79-5108
Moisiadi, S. A., 79-5196
Moldoveanu, N., 79-5183
Mole, R. H., 79-4859
Moller, R., 79-5390
Monne, J., 79-5331
Monrozier, X., 79-5089
Moore, C. J., 79-5058
Moore, M. R., 79-4814
Moore, R., 79-5259
Moore, W. S., 79-5307
Morahan, P. S., 79-5194
Moretti, A., 79-5340
Morgan, A. C., 79-5239
Mori, H., 79-5035
Morin, J., 79-5034
Morita, M., 79-5096
Moriwaki, S., 79-5380
Morris, A. G., 79-5129
Morrison, A. S., 79-5353
Morse, L. S., 79-4885, 79-5189
Morton, K. S., 79-5319
Mossanda, K., 79-5066
Mowat, A. G., 79-5333
Moyer, G. H., 79-4986
Mukojima, T., 79-5165
Muller, G., 79-4944
Muller, W. E., 79-5176
Munck, V., 79-5203
Munk, K., 79-4875, 79-4911, 79-5192
Muntz, E. P., 79-4863
Muntzing, J., 79-5046
Murata, Y., 79-5140
Murray, J. M., 79-5345
Murray, K., 79-5208
Musiani, P., 79-4901
Myers, M., 79-4922
Myers, R. T., 79-5348
Myerson, D., 79-5141
Nabokov, Iu. S., 79-5226

- Nachtigal, M., 79-5183
 Nachtigall, L. E., 79-5354
 Nachtigall, R. D., 79-5354
 Nachtigall, R. H., 79-5354
 Nagao, S., 79-5311
 Nahmias, A. J., 79-4877
 Naito, H., 79-5339, 79-5378
 Nakamura, K., 79-5109
 Nakashima, K., 79-5352
 Nakayama, T., 79-5378
 Nakayama, Y., 79-5378
 Naor, D., 79-4903
 Nasim, A., 79-4953
 Navickis, R. J., 79-5080
 Nayar, K. T., 79-5127
 Nazerian, K., 79-5124
 Nebert, D. W., 79-4840, 79-5062
 79-5063, 79-5073
 Neel, E. U., 79-5170
 Neiman, R. S., 79-5272
 Nelson, S. D., 79-5022
 Nemoto, N., 79-5064
 Neville, A. M., 79-5280
 Newcomb, M. M., 79-5318
 Nicholas, A. H., 79-4971
 Nielsen, T., 79-5105
 Niho, Y., 79-5326
 Nikoskelainen, J., 79-5170
 Nilsson, K., 79-4891, 79-5164
 Nilsson, S., 79-5387
 Nishimoto, A., 79-5311
 Nishiyama, Y., 79-4982
 Nissen-Druey, C., 79-5296
 Nissenkorn, I., 79-5083
 Nkrumah, F., 79-5167
 Norkin, L. C., 79-5221
 Norman, D., 79-4837
 Norrild, B., 79-5190
 Nosaka, Y., 79-5311
 Novotna, E., 79-5375
 O'Brien, P. J., 79-5074
 O'Kech, N., 79-5259
 O'Reilly, G., 79-5337
 Oakes, J. E., 79-4887
 Obalek, S., 79-5172
 Oesch, F., 79-5078
 Ogino, T., 79-5284
 Oguma, N., 79-5096
 Ohnuma, T., 79-5392
 Ohta, N., 79-5381
 Ohtawa, M., 79-5008
 Oka, M., 79-5352
 Okabe, M., 79-5339, 79-5378
 Okasinski, G. F., 79-4896
 Oku, T., 79-5284
 Okunewick, J. P., 79-4952
 Old, L. J., 79-5276
 Oldstone, M. B., 79-5228
 Oliver, J. E., 79-4827
 Olson, C., 79-5156
 Olszyna-Marzys, A. E., 79-5032
 Omi, Y., 79-5381
 Ono, J., 79-5326
 Oohashi, H., 79-5335
 Oohashi, Y., 79-5036
 Oota, T., 79-5304
 Oranje, A. P., 79-5349
 Orfanos, C. E., 79-5321
 Orth, G., 79-5172
 Osato, T., 79-5161, 79-5163
 Osechin'skii, I. V., 79-5384
 Osman, M. I., 79-5233
 Ostertag, W., 79-5130
 Pack, G., 79-5038
 Pagano, J. S., 79-4896, 79-5169
 Page, G. V., 79-4974
 Panda, B. B., 79-5027
 Panem, S., 79-5264
 Pant, G. S., 79-5096
 Papadopoulos, D., 79-4967
 Paquin, F., 79-5351
 Pardatscher, K., 79-5314
 Park, J. F., 79-5106
 Parker, J., 79-5204
 Parodi, S., 79-4999
 Pashkevich, K. I., 79-5020
 Patterson, D. S., 79-5030
 Patterson, M., 79-5088
 Patton, J. T., 79-5155
 Paul, J., 79-5130
 Pavliuchenkova, R. P., 79-5226
 Pawlowski, A., 79-5271
 Payne, W. S., 79-5124
 Pearson, L., 79-4845
 Pelkonen, O., 79-5062, 79-5063
 Pellone, M., 79-5314
 Pembroke, A. C., 79-4861
 Pereira, L., 79-5189
 Perevozchikov, A. P., 79-5224
 Perez, M., 79-5248
 Perkins, J. P., 79-5072
 Peterson, L. E., 79-5387
 Pfeiffermann, R., 79-5114
 Philipp, E. E., 79-5347
 Phillips, J., 79-5038
 Phillips, J. C., 79-4989
 Piantelli, M., 79-4901
 Pienta, R. J., 79-4984
 Pierce, E., 79-5112
 Pierce, E. H., 79-5338
 Pike, M. C., 79-5258
 Pilawska, H., 79-5366
 Pilkington, G. J., 79-4980
 Pimenova, V. V., 79-4824
 Pinnock, M. H., 79-4956
 Podobed, O. V., 79-5057
 Polani, P. E., 79-5277
 Pollak, A., 79-5316
 Pollard, R. B., 79-5159
 Poncelet, F., 79-5066
 Pope, J. H., 79-4872
 Portoukalian, J., 79-5399
 Porzig, K. J., 79-5151
 Potter, M., 79-5238
 Poukka Evarts, R., 79-5049
 Pour, P., 79-4991
 Powell, D., 79-4850
 Power, L. H., 79-5337
 Powers, G. J., 79-5106
 Pozharisskii, K. M., 79-4918
 Pragnell, I. B., 79-5130
 Prehn, R. T., 79-5053
 Pressler, H., 79-5242
 Preston, C. M., 79-4884
 Preston, V., 79-5188
 Price, J. E., 79-5344
 Prins, H. W., 79-4945
 Proctor, J. W., 79-5278
 Pruitt, B. A., 79-4860
 Prunieras, M., 79-5398
 Prusoff, W. H., 79-5180
 Pueyo, C., 79-4988
 Purchase, I. F., 79-4917
 Puricelli, L., 79-5241
 Pushpendran, C. K., 79-4969
 Queval, P., 79-5025
 Quiviger, P., 79-5086
 Rabinowitz, S. G., 79-5232
 Radovich, J., 79-5273
 Rahimtula, A. D., 79-5074
 Raikow, R. B., 79-4952
 Rakusanova, T., 79-5209
 Rall, D. P., 79-4806
 Ramel, C., 79-4801
 Ramselaar, C. G., 79-5045
 Rand, K. H., 79-5159
 Ranelletti, F. O., 79-5087
 Rao, A. B., 79-5388
 Rao, D. N., 79-5238
 Rapp, F., 79-4870, 79-4887
 Rapson, N., 79-5267
 Raska, K., 79-5201
 Rasmussen, L. E., 79-5159
 Rauber, G., 79-5374
 Rauert, K., 79-5250
 Rawlins, M. D., 79-5277
 Rawls, R. L., 79-4802
 Ray, V., 79-4801
 Reed, C. D., 79-5137
 Reed, P. I., 79-5040
 Reeve, N. L., 79-4855
 Regnier, M., 79-5398
 Reid, T. W., 79-5147, 79-5148
 Reimer, R. R., 79-4995
 Reiss-Gutfreund, R. J., 79-5187
 Rendina, G. M., 79-5383
 Reuber, M. D., 79-5023
 Reuveni, Y., 79-5210
 Reymann, F., 79-5390
 Richart, C., 79-5331
 Rickart, R., 79-4990
 Rickert, R. R., 79-5329
 Rickinson, A. B., 79-5168
 Rieder, V., 79-5217
 Riggs, C. W., 79-5137
 Rigobello, L., 79-5314
 Rijnders, R. F., 79-4833
 Rinsky, R. A., 79-5358
 Riondet, J., 79-4924
 Risebrough, R. W., 79-5098
 Rivenson, A., 79-4853
 Rizki, R. M., 79-5282
 Rizki, T. M., 79-5282
 Roberts, B. A., 79-5030
 Roberts, L. K., 79-5099
 Roberts, M., 79-5102
 Roberts, W. C., 79-5320
 Robey, P. G., 79-5317
 Robinette, C. D., 79-5356
 Robinson, H. L., 79-5118
 Robinson, W. A., 79-5288

Rodova, O., 79-5376
 Rodriguez-Lopez, F., 79-4895
 Roe, F. J., 79-4942, 79-5039
 Roizman, B., 79-4885, 79-5189
 Rooke, G. B., 79-5371
 Rosch, P. J., 79-4934
 Roscoe, J. P., 79-4979
 Rosen, A., 79-5165
 Rosen, N., 79-5136
 Rosenberg, L., 79-5362
 Rosenkranz, H. S., 79-4954
 Rosenthal, L. J., 79-5210
 Ross, J. S., 79-4955
 Rossen, R. D., 79-5239
 Rossi, H. H., 79-4859
 Rothman, K. J., 79-4932
 Rowland, J., 79-4947
 Rubin, P., 79-5040
 Ruddell, W. S., 79-5040
 Rudikoff, S., 79-5238
 Ruibal, A., 79-5331
 Ruscetti, S. K., 79-5131
 Russell, J. M., 79-5348
 Russell, P., 79-5147, 79-5148
 Rutledge, F., 79-5231
 Ruttner, J. R., 79-5377
 Ryan, D. E., 79-5060
 Ryan, W., 79-5256
 Rymgaylo, B., 79-5366
 Rzeska, G., 79-5172
 Saarni, H., 79-5062
 Saavedra, J. E., 79-4821, 79-4997
 Safo, M. H., 79-5252
 Sahu, R. K., 79-5027
 Saita, B., 79-5352
 Sakakibara, K., 79-5304
 Sakuma, A., 79-5379
 Sakuma, T., 79-5055
 Salamone, M. F., 79-5059
 Salsano, F., 79-4901
 Salvatore, K. J., 79-5237
 Salzman, L. A., 79-5146
 Samoilenko, L. A., 79-4849
 Samucha, R., 79-5136
 Saperstein, M. D., 79-5067
 Sarmiento, M., 79-4869
 Sasai, K., 79-5284
 Sasse, W., 79-5254
 Sato, R., 79-4965
 Sauer, H. D., 79-4977
 Savi, M., 79-4835
 Savost'ianov, G. A., 79-5224
 Saw, H. S., 79-5368
 Sawada, T., 79-5255
 Schaffer, P. A., 79-4871, 79-5189
 Scheid, A., 79-5229
 Scheinberg, D., 79-5141
 Scheuer, A., 79-4847
 Schick, J., 79-5198
 Schick, P., 79-5250
 Schilling, J., 79-5265
 Schlatter, C., 79-5061
 Schlehofer, J. R., 79-5185
 Schmidt, J., 79-5310
 Schmidt-Ullrich, R., 79-5218
 Schmitt, M., 79-5099
 Schneider, E. L., 79-4941

Schneiderman, M. A., 79-4831
 Scholz, S., 79-5306
 Schottenfeld, D., 79-4919
 Schreiber, H., 79-5264
 Schrier, S. L., 79-5293
 Schroder, C. H., 79-5174
 Schroder, G., 79-5332
 Schuler, D., 79-4994
 Schuller, P. L., 79-4828
 Schumaker, J. A., 79-4845
 Schumrick, D., 79-5355
 Schuster, P., 79-5242
 Schut, L., 79-5312
 Schwaier, A., 79-5192
 Schwartz, S. A., 79-5135, 79-5225
 Schwarz, M., 79-4990
 Sciaba, L., 79-4999
 Scolnick, E. M., 79-5131, 79-5151
 Seeman, P. R., 79-4952
 Seffert, P., 79-5086
 Seid, D. A., 79-5014
 Seigel, D., 79-4922
 Seits, I. F., 79-5224
 Sekiguchi, M., 79-5304
 Sekiya, S., 79-5051
 Selevan, S. G., 79-5363
 Seligmann, M., 79-4900
 Senula, G. C., 79-4941
 Serdobol'ski, V. I., 79-5384
 Servadio, C., 79-5083
 Setokuchi, T., 79-5092
 Shafeek, M. A., 79-5233
 Shaheen, A., 79-5252
 Shanley, J. D., 79-5158
 Shapiro, A., 79-5114
 Shapiro, S., 79-5362
 Sharma, C. B., 79-5027
 Shattuck, D. M., 79-5230
 Shaw, H. M., 79-5016
 Shaw, J. E., 79-5169
 Shelby, M. D., 79-4804
 Shenk, T., 79-5213
 Sherbet, G. V., 79-5220
 Shevchuk-Chaban, M., 79-5193
 Shevliaghin, V., 79-5206
 Shibuya, T., 79-5326
 Shiina, Y., 79-5350
 Shillito, E. J., 79-4870, 79-5181
 Shimada, T., 79-4965
 Shin, S., 79-5261
 Shoyab, M., 79-5044
 Shreeve, B. J., 79-5030
 Shultz, K. L., 79-5237
 Shuster, S., 79-5277
 Sibley, C., 79-5265
 Siebert, D., 79-5009
 Siegler, A. M., 79-4921
 Sigaran, M. F., 79-5001
 Silagi, S., 79-5231
 Silvergleid, A., 79-5010
 Silverman, J., 79-4853
 Silverstein, S., 79-5178
 Silvis, S. E., 79-5076
 Simonis, R. F., 79-5302
 Singh, S., 79-4821
 Sinks, L. F., 79-4925
 Siou, G., 79-4957

Sippel, W. G., 79-5306
 Skoryna, S. C., 79-4951
 Skrabanek, P., 79-4850
 Skucinski, S., 79-5366
 Slankard-Chahinian, M., 79-5392
 Sliski, A. H., 79-5152
 Slone, D., 79-5362
 Sloper, R. W., 79-5093
 Smales, W. P., 79-5209
 Smirnova, I. N., 79-5322
 Smit, A. F., 79-5349
 Smith, B., 79-4988
 Smith, E. J., 79-5118
 Smith, P. G., 79-5267
 Smits, P. J., 79-5302
 Snyderman, R., 79-5258
 Sofos, J. N., 79-4975
 Solberg, L. A., 79-4948
 Solberg, M., 79-4974
 Solomon, A., 79-5328, 79-5334
 Solomon, F., 79-5251
 Sonstegard, K. S., 79-4881
 Sonstegard, R. A., 79-4881
 Soroka, M., 79-5366
 Sorsa, M., 79-5090
 Soto, H., 79-5017
 Southern, L. L., 79-5031
 Sparke, B., 79-5388
 Spear, P. G., 79-4869
 Speck, B., 79-5296
 Spicer, S. S., 79-5297
 Sprinkle, P. M., 79-5171
 Squire, R. A., 79-5400
 Stanovick, R. P., 79-5024
 Steinberg, M. H., 79-5318
 Steinhorn, S. C., 79-4922
 Stenback, F., 79-4947, 79-5256
 Stephany, R. W., 79-4828
 Stevens, D. A., 79-5170
 Stevens, J. G., 79-4878, 79-5150
 79-5158
 Stevens, S., 79-5091
 Stockle, G., 79-4962
 Stolley, P. D., 79-5362
 Stolz, E., 79-5349
 Stout, E. R., 79-5155
 Stow, N. D., 79-5188
 Strain, A. J., 79-5280
 Strand, M., 79-5141
 Stringer, J. R., 79-5177
 Studd, J. W., 79-5088
 Stutman, O., 79-5260
 Subak-Sharpe, J., 79-5186
 Subak-Sharpe, J. H., 79-5188
 Sugahara, N., 79-5379
 Sugimoto, T., 79-5255
 Sugiyama, H., 79-5140
 Sulser, H., 79-5377
 Sumer, T., 79-4925
 Summers, W. C., 79-5180
 Summers, W. P., 79-5180
 Sun, A. S., 79-5392
 Sundaram, K., 79-4801
 Sundh, K., 79-4958
 Sundquist, B., 79-5154
 Suzuki, K., 79-5381
 Svardsudd, K., 79-5386

- Swaminathan, A. P., 79-5329
 Sydnor, K. L., 79-5065
 Syrowatka, T., 79-4963
 Szekely, A. M., 79-5034
 Tabuchi, K., 79-5311
 Tadeusiak, B., 79-4963
 Taguchi, F., 79-5142
 Tajima, A., 79-5381
 Takada, K., 79-5161, 79-5163
 Takahashi, M., 79-5035, 79-5284
 Takahashi, S., 79-5011
 Takahashi, T., 79-5276
 Takaki, R., 79-5326
 Takamizawa, H., 79-5051
 Takashima, S., 79-5380
 Takasu, T., 79-5007
 Takayama, S., 79-5002, 79-5064
 Takeda, B., 79-5051
 Takita, M., 79-5011
 Talmage, D. W., 79-5273
 Tanaka, A., 79-4970
 Tanaka, R., 79-5096
 Tanaka, T., 79-5035
 Tanasescu, D., 79-5183
 Tani, S., 79-5284
 Tao, T., 79-5323
 Tarin, D., 79-5344
 Tatsuguchi, K., 79-5092
 Tay, L. K., 79-5065
 Taylor, C. R., 79-5294
 Taylor, R. T., 79-4949
 Taylor, T. V., 79-5040
 Tchao, R., 79-5395
 Tennant, R. W., 79-5139
 Tevethia, M. J., 79-5217
 Tevethia, S. S., 79-5217
 Thakker, D. R., 79-5060
 Theilen, G. H., 79-5156
 Theis, G. A., 79-5123
 Therkelsen, A. J., 79-5203
 Thiel, E., 79-5268
 Thimmappaya, B., 79-5213
 Thimmig, R. L., 79-5232
 Thom, M., 79-5088
 Thomas, P. E., 79-5060
 Thompson, W. S., 79-5218
 Thomson, S. V., 79-5028
 Thurner, J., 79-4913
 Tibblin, G., 79-5386
 Tickle, C., 79-4979
 Tikhonova, N. A., 79-4849
 Till, M., 79-5267
 Timbury, M. C., 79-5188
 Tinnefeld, W., 79-5242
 Tipping, E., 79-4985
 Tisdale, M. J., 79-4937
 Tomatis, L., 79-4817
 Tometsko, A. M., 79-5005
 Tometsko, J. G., 79-5005
 Tooze, J., 79-5208
 Torjussen, W., 79-4948
 Torralba, G., 79-5100
 Torras, P., 79-5034
 Torres, M. D., 79-5248
 Tovey, M. G., 79-5173
 Toyos, J. M., 79-5346
 Toyoshima, K., 79-5140
 Tozawa, M., 79-5255
 Trasti, H., 79-5387
 Travassos, L. R., 79-5276
 Treisman, R., 79-5204
 Trichopoulos, D., 79-4898
 Trofater, K. F., 79-5195
 Trosko, J. E., 79-4909
 Troxler, D., 79-5131
 Truhaut, R., 79-4805
 Truscott, T. G., 79-5093
 Tsambaos, D., 79-5321
 Tucker, M. J., 79-5397
 Tupalska, M., 79-5365
 Turujman, S., 79-5060
 Twardzik, D. R., 79-5137
 Twomey, J. J., 79-5239
 Tytgat, G. N., 79-5111
 U. S. Department of Health, Education,
 and Welfare
 79-4830
 Ulland, B. M., 79-4960
 Ullman, B., 79-5396
 Ulrich, C. E., 79-4976
 Umeda, M., 79-5026
 Umezawa, I., 79-4982
 Uriel, J., 79-4899
 Ushimaru, Y., 79-5035
 Vainio, H., 79-5090
 Van Beveren, C., 79-5132
 Van De Staak, W. J., 79-5222
 Van Den Berghe, H., 79-4971
 Van den Hamer, C. J., 79-4945
 van den Tweel, J. G., 79-5294
 van der Meer, J. B., 79-5045
 van der Woerd-de Lange, J. A.
 79-5250
 Van Heuverswyn, H., 79-5212
 Varas Lorenzo, M. J., 79-4912
 Varesio, L., 79-5246
 Vawter, G. F., 79-5289
 Veltri, R. W., 79-5171
 Venkatesan, N., 79-5100
 Vennes, J. A., 79-5076
 Venske, G., 79-4981
 Verwoerd, D. W., 79-5153
 Vestergaard, B. F., 79-5190
 Vienne, M., 79-4971
 Vignal, J., 79-5086
 Vinuela, A., 79-5346
 Virmani, R., 79-5320
 Voelker, R. W., 79-5024
 Vogel, H., 79-5385
 Vogel, K., 79-5323
 Vogel, S. B., 79-5076
 Volckaert, G., 79-5214
 Von Melchner, H., 79-5257
 Vutuc, C., 79-5389
 Vuzevski, V., 79-5349
 Wadell, G., 79-5197
 Wagner, E. K., 79-5177
 Wagner, R. R., 79-5230
 Wagoner, J. K., 79-5358, 79-5363
 79-5364
 Wakabayashi, K., 79-5036
 Wake, N., 79-5350
 Walker, A. M., 79-4932
 Walker, C. H., 79-5068
 Walker, J., 79-5180
 Wallach, D. F., 79-5218
 Wallner, S. F., 79-5288
 Walrath, D. C., 79-5113
 Walter, G., 79-5199
 Walters, C. L., 79-5040
 Wan, C. W., 79-5143
 Wang, C. F., 79-4921
 Ward, F. G., 79-5371
 Ward, J. M., 79-5400
 Warner, G. A., 79-5263
 Warner, T. F., 79-5337
 Warpeha, R., 79-5108
 Warren, K. G., 79-5186
 Watanabe, T., 79-5092
 Watkins, J. B., 79-4955
 Watkins, R. N., 79-4932
 Waxweiler, R. J., 79-5364
 Weck, P. K., 79-5230
 Wegener, K., 79-5110
 Wei, E. T., 79-5014
 Weichert, K. A., 79-5355
 Weil, J., 79-5306
 Weinstein, I. B., 79-4838, 79-5077
 Weinstein, R. S., 79-4914
 Weisburger, J. H., 79-4927
 Weislow, O. S., 79-5137
 Weissmann, R. A., 79-5107
 Weissmann, C., 79-5208
 Welch, R. M., 79-4818
 Wenzel, J., 79-5187
 Werner-Favre, C., 79-5247
 Westphal, H., 79-5199
 Wettstein, F. O., 79-5150
 Whalley, H. E., 79-4964
 Wheeler, L. A., 79-5067
 Whitaker, C. J., 79-5371
 Whitlock, J. P., 79-4839
 Whittaker, N., 79-5060
 Wiener, J. D., 79-5301
 Wilbourn, J. D., 79-4817
 Wilkie, N. M., 79-4867, 79-5188
 Williams, D. C., 79-4956
 Williams, D. D., 79-5283
 Williams, R. J., 79-5195
 Williamson, R., 79-5130
 Williamson, R. C., 79-4955
 Wilson, G., 79-5162
 Wilton, J. M., 79-5181
 Witeska, A., 79-5342
 Wolf, H., 79-4879
 Wolf, S. J., 79-5244
 Wolfe, J., 79-5364
 Wolff, S., 79-4829
 Wolters, E. A., 79-5245
 Wood, A. W., 79-5060
 Wood, D. J., 79-5361
 Wood, W. S., 79-5104
 Wroblewska, Z., 79-5186
 Wu, R., 79-4949
 Wyke, J. A., 79-5117
 Wynder, E. L., 79-4928
 Yagi, H., 79-5060
 Yamada, J., 79-5092
 Yamaha, T., 79-4970
 Yamamoto, M., 79-5335
 Yamamoto, T., 79-4942, 79-4943

Yamane, Y., 79-5008
Yamawaki, Y., 79-5335
Yanbe, T., 79-5379
Yardley, J. H., 79-5343
Yee, D., 79-5160
Yeh, M. Y., 79-5263
Yoder, S., 79-4821
Yoshida, K., 79-5378
Yoshikura, H., 79-5142

Yosida, T. H., 79-5140
Young, R. J., 79-5358
Yuasa, Y., 79-4943
Yutsudo, M., 79-5140
Zachariah, P. K., 79-5074
Zachwiej, J., 79-5342
Zahn, R. K., 79-5176
Zawadzki, Z. A., 79-5272
Zenobi, R., 79-5087

Zhudina, A. I., 79-5224
Zhukova, G. F., 79-4824
Zickerman, P., 79-5112, 79-5338
Zinns, J. S., 79-4939
Ziolkowski, C. H., 79-5200
Zober, A., 79-4946
Zouzias, D., 79-5216
zur Hausen, H., 79-4889, 79-4892

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1. The first part of the paper is devoted to a general discussion of the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β . It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

2. In the second part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

3. In the third part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

4. In the fourth part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

5. In the fifth part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

6. In the sixth part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

7. In the seventh part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

8. In the eighth part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

9. In the ninth part of the paper the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β is solved. It is shown that the system has solutions for arbitrary values of the parameters α and β if and only if the condition $\alpha + \beta = 1$ is satisfied.

Subject Index

Abnormalities

- Benz(a)anthracene, 7,12-Dimethyl-
Ovary, Testis, Mouse, 79-5050
- 4,4'-Stilbenediol, α, α' -Diethyl-
Reproductive Dysfunction, Review, 79-4921
- Sweat Gland Neoplasms
Fingers, Toes, 79-5321
- Thymus Gland
Rat, Nude, 79-5259
- Urea, Ethyl Nitroso-
Ependyma, Rat, 79-4980

Acanthosis Nigricans

- Uterine Neoplasms
Adenocarcinoma, 79-5349
Case Report, 79-5349

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

- DNA, Binding
Liver, Rat, 79-4986
- DNA Repair
Chromatids, Review, 79-4829
- RNA Polymerase
Enzyme Inactivation, 79-4986
- RNA Replication
Liver, Rat, 79-4986

Acetamide, *N*-(Carbamoylmethyl)-2-diazo-

- DNA Repair
Cells, Cultured, 79-4999

Acetamide, *N*-Fluoren-2-yl-

- Ames Test
Mutagenic Metabolite, 79-4963
- Bladder Neoplasms
Carcinoma, 79-4864
- Carrier Proteins
Cell Membrane, 79-4985
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
Mutagenic Metabolite, 79-4963
- Liver Neoplasms
Fetal Globulins, 79-4907
Immune Response, Review, 79-4907
- Phosphatidylcholines
Membranes, Binding, 79-4985
- Urine
Mutagenic Metabolite, 79-4963

Acetic Acid, (Ethylenedinitrilo)tetra-

- Benz(a)anthracene, 7,12-Dimethyl-
DNA, Binding, 79-5044
- Escherichia coli*
Lipopolysaccharides, 79-5092
- Stannane, Chlorotripropyl-
Antibacterial Activity, 79-5092
- Stannane, Tributylchloro-
Antibacterial Activity, 79-5092

Acetic Acid, Lead Salt

- Kidney Neoplasms
Carcinogenic Potential, Review, 79-4814
- 2-Pyrrolidine, 1-nitroso-, Acetate (Ester)
Synthesis, 79-4997

Acetic Acid, Mercapto-

- Lung Neoplasms
Macrophages, 79-5257

Acetic Acid, (2,4,5-Trichlorophenoxy)-

- Chromosome Aberrations
Teratogenic Effects, Review, 79-4832
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Teratogenic Effects, Review, 79-4832
- Drosophila*
Mutagenic Activity, Review, 79-4832
- Neoplasms, Experimental
Dose-Response Study, Mouse, Review, 79-4832
- Saccharomyces cerevisiae*
Mutagenic Activity, Review, 79-4832

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

- RNA Replication
Liver, Rat, 79-4986

p-Acetophenetidine, *N*-Hydroxy-

- Nitroso Compounds
Metabolism, Review, 79-4818

p-Acetophenetidine

- Diet
Nitrosation, Review, 79-4818
- Kidney Neoplasms
Carcinoma, Transitional Cell, 79-5006
Case Report, 79-5006
- Nitroso Compounds
Metabolism, Review, 79-4818
- Transplacental Carcinogenesis
Epidemiology, Review, 79-4815

Acromegaly

- Brain Neoplasms
Radiotherapy, 79-5102

Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-

- DNA Repair
Escherichia coli, 79-5000
Escherichia coli
Mutagenic Activity, 79-5000

Actin

- Neuroblastoma
Isolation and Characterization, 79-5394
- Virus, SV40
Cell Adhesion, 79-5219

Actinomycin D

- Aryl Hydrocarbon Hydroxylases
Enzyme Induction, Review, 79-4839

Adenine

- Neuroblastoma
Homocysteine, *S*-Adenosyl-, 79-5393
Metabolism, 79-5393

Adenine Nucleotides

- Benzo(a)pyrene, 6-Acetoxyethyl-
Carcinogenic Metabolite, 79-5065
- Benzo(a)pyrene-6-methanol
Carcinogenic Metabolite, 79-5065

Adenocarcinoma

- Benzenamine, 4,4'-Methylenebis(2-chloro)-
Dose-Response Study, Rat, 79-5024
- Bladder Neoplasms
Precancerous Conditions, 79-5341
- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
Asbestos, 79-4978

Adenocarcinoma (cont'd)

- Cervix Neoplasms
 - Estradiol, 79-5075
 - Prolactin, 79-5075
- Colonic Neoplasms
 - Hydrazine, 1,2-Dimethyl-, 79-4977
 - Methane, Azoxy-, 79-4955
 - Urinary Diversion, 79-5112, 79-5113, 79-5338
- Digestive System Neoplasms
 - Neoplasms, Multiple Primary, 79-5348
 - Panfuran-S, 79-5011
- Fibrinolysis
 - Neoplasm Metastasis, 79-5307
- Histocompatibility Antigens
 - Transplantation Immunology, 79-5246
- Intestinal Neoplasms
 - Bracken Fern, 79-5035
 - Neoplasm Transplantation, 79-5035
 - Polyps, 79-4913
- Kidney Neoplasms
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 79-5083
 - Transplantation, Heterologous, 79-5280
- Leukocytes
 - Histocompatibility Antigens, 79-5246
- Lung Neoplasms
 - Air Pollutants, 79-5019
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
 - Chromium, 79-4946
 - Sex Chromosome, 79-5327
 - Smoking, 79-5368
 - Tuberculosis, Pulmonary, 79-5328
- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-4918
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
 - Ethane, 1,2-Dichloro-, 79-4961
- Neoplasms, Multiple Primary
 - Case Report, 79-5348
- Pancreatic Neoplasms
 - Neoplasm Metastasis, 79-5302
- Peritoneal Neoplasms
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Prostatic Neoplasms
 - Animal Models, Review, 79-4853
 - Carcinogen, Chemical, 79-4853
 - Radiation, Ionizing, 79-4853
 - Virus, SV40, 79-4853
- Rectal Neoplasms
 - Polyps, 79-5343
- Stomach Neoplasms
 - Gastrectomy, 79-5111
- Testicular Neoplasms
 - Paget's Disease, Extra-Mammary, 79-5352
- Urogenital Neoplasms
 - Neoplasms, Multiple Primary, 79-5348
- Uterine Neoplasms
 - Acanthosis Nigricans, 79-5349
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5051
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester 79-4978
 - Phosphoric Acid, Trimethyl Ester, 79-4816
- Virus, Herpes
 - Cells, Cultured, Review, 79-4870
- Virus, Herpes Simplex 1
 - Histocompatibility Antigens, 79-5184
 - Neoplasm Metastasis, 79-5184

Adenocarcinoma, Papillary

- Intestinal Neoplasms

Adenocarcinoma, Papillary (cont'd)

- Methane, Azoxy-, 79-4955

- Lung Neoplasms
 - Epidemiology, 79-5370

Adenofibroma

- Mammary Neoplasms, Experimental
 - Epidemiology, Rat, 79-5400
- Ovarian Neoplasms
 - Epidemiology, 79-5382

Adenoma

- Brain Neoplasms
 - Neoplasm Metastasis, 79-5298
- Colonic Neoplasms
 - Hydrazine, 1,2-Dimethyl-, 79-4977
- Dibenz(a,h)acridine
 - Iron Oxide, 79-4947
- Liver Neoplasms
 - Androgens, 79-4847
 - Contraceptives, Oral, 79-4931, 79-5089
 - Estradiol, 17-Ethynyl-, 79-5086
 - Ethynodiol Diacetate, 79-5086
 - Mestranol, 79-5089
 - Norethisterone Acetate, 79-5086
- Lung Neoplasms
 - Air Pollutants, 79-5019
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
 - Methane, Nitro-, 79-5018
 - Urea, Ethyl Nitroso-, 79-4982
- Mammary Neoplasms, Experimental
 - Diet, 79-5397
- Pituitary Neoplasms
 - Diet, 79-5397
 - Epidemiology, Rat, 79-5400
 - Neoplasm Metastasis, 79-5298
- Respiratory Tract Neoplasms
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester 79-4978
- Thyroid Neoplasms
 - Hyperthyroidism, 79-5301

Adenomatosis, Familial Endocrine

- Pancreatic Neoplasms
 - Case Report, 79-5309
 - Diarrhea, 79-5309
 - Islet Cell Tumor, 79-5309

Adenosine

- Neuroblastoma
 - Metabolism, 79-5393

Adenosine Cyclic 3',5' Monophosphate

- Astrocytoma
 - Isoproterenol, 79-5072
 - Prostaglandins E, 79-5072
- Carcinogen, Chemical
 - Metabolism, Review, 79-4937
- DNA Repair
 - Cell Transformation, Neoplastic, Review, 79-4937
- Neoplasms, Experimental
 - Growth, Review, 79-4937
- Oncogenic Viruses
 - Cell Transformation, Neoplastic, Review, 79-4937
- Prostaglandins
 - Graft Rejection, 79-4842

Adenosine Triphosphatase

- Benzo(a)pyrene
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-5064

- Adenosine Triphosphatase (cont'd)**
 - Hepatocarcinogenesis, 79-5064
- Cycloheximide
 - Microsomes, Liver, 79-4969
- Ethylene, Chloro-
 - Hepatocarcinogenesis, 79-4962
- Ethylene, 1,1-Difluoro-
 - Hepatocarcinogenesis, 79-4962
- Adenosine Triphosphate**
 - Benzo(a)pyrene, 6-Acetoxyethyl-DNA, Binding, 79-5065
 - Benzo(a)pyrene-6-methanol DNA, Binding, 79-5065
- Adenyl Cyclase**
 - Astrocytoma
 - Isoproterenol, 79-5072
 - Prostaglandins E, 79-5072
 - Oncogenic Viruses
 - Cell Transformation, Neoplastic, Review, 79-4937
- Adipose Tissue**
 - Hemocytes
 - Phagocytosis, 79-5282
 - Neoplasms, Experimental
 - Drosophila melanogaster*, 79-5282
- Adrenal Cortex**
 - 7,8-Benzoflavone
 - Aryl Hydrocarbon Hydroxylases, 79-5073
 - Cholanthrene, 3-Methyl-
 - Aryl Hydrocarbon Hydroxylases, 79-5073
 - Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Aryl Hydrocarbon Hydroxylases, 79-5073
- Adrenal Gland Neoplasms**
 - Neuroblastoma
 - Cell Line, 79-5304
 - Ultrastructural Study, 79-5304
 - Paraganglioma
 - Raynaud's Disease, 79-5308
 - Pheochromocytoma
 - Raynaud's Disease, 79-5308
- Adriamycin**
 - Leukemia, Myeloblastic
 - Radiation, Ionizing, 79-4995
- Aflatoxin B1**
 - Bacteria
 - Phagocytosis, 79-5033
 - Food Contamination
 - Milk, 79-5030
 - Weather, 79-5032
 - Hepatoma
 - Portocaval Shunt, 79-5034
 - Leukocytes
 - Chemotaxis, 79-5033
 - Phagocytosis
 - Heterophils, Chick, 79-5033
- Aflatoxin G1**
 - Food Contamination
 - Weather, 79-5032
- Aflatoxin G2**
 - Food Contamination
 - Weather, 79-5032
- Aflatoxin M1**
 - Food Contamination
- Aflatoxin M1 (cont'd)**
 - Milk, 79-5030
- Agammaglobulinemia**
 - Hodgkin's Disease
 - Immunologic Deficiency Syndromes, 79-5266
 - IgG
 - Case Report, Child, 79-5266
- Agar**
 - Respiratory Tract Neoplasms
 - Benzo(a)pyrene, 79-4947
- Aging**
 - Nucleotidases
 - Lymphocytes, 79-5392
 - Nucleotides, 79-5392
- Air Pollutants**
 - Hepatoma
 - Carcinogen, Chemical, 79-5019
 - Lung Neoplasms
 - Adenocarcinoma, 79-5019
 - Adenoma, 79-5019
 - Lymphoma
 - Carcinogen, Chemical, 79-5019
- Air Pollution**
 - Arsenic
 - Canada, Review, 79-4812
 - Asbestos
 - Canada, Review, 79-4812
 - Benzo(a)pyrene
 - Spectrum Analysis, 79-5055
 - Polycyclic Hydrocarbons
 - Spectrum Analysis, 79-5055
 - Respiratory Tract Neoplasms
 - Benzo(a)pyrene, 79-5366
- Alcohol Oxidoreductases**
 - Benzoic Acid, *p*-Nitro-
 - Ethyl Alcohol, 79-5004
- Alkaline Phosphatase**
 - Leukemia, Myeloblastic
 - Precancerous Conditions, 79-5291
 - Phosphatidylinositols
 - Cell Membrane, 79-4835
 - 4,4'-Stilbenediol, α,α' -Diethyl-
 - Calcium, 79-5082
- Alkylating Agents**
 - Structure-Activity Relationship
 - Carcinogenic Metabolite, Review, 79-4920
- Alpha 1-Antitrypsin**
 - Hepatoma
 - Immunocytochemical Study, 79-5330
- Alpha Fetoproteins**
 - Cell Transformation, Neoplastic
 - Retrodifferentiation, Review, 79-4899
- Aluminum Chloride**
 - Quinoline, 4-(Hydroxyamino)-, 1-Oxide
 - DNA, Binding, 79-5008
 - Nucleotides, Binding, 79-5008
- α -Amanitine**
 - Virus, Adeno 12
 - RNA Replication, 79-5201
 - Virus, Bovine Parvo
 - RNA Replication, 79-5155

Americium

- Body Burden
 - Inhalation Study, Dog, 79-5106
- Bone and Bones
 - Body Burden, 79-5106
- Liver
 - Body Burden, 79-5106

Ames Test

- Acetamide, *N*-Fluorene-2-yl-
 - Mutagenic Metabolite, 79-4963
- Antineoplastic Agents
 - Mutagenic Metabolite, 79-5090
- Benz(e)acephenanthrylene
 - Food Contamination, 79-5066
- Benzene, 4-Azido-1,3-dinitro-
 - Dose-Response Study, 79-5005
- Benzene, 4-Azido-1-Fluoro-2-nitro-
 - Dose-Response Study, 79-5005
- Benzo(a)pyrene
 - S9-Fraction, 79-5059
- Benzo(e)pyrene
 - Aroclor 1254, 79-5060
 - Microsomes, Liver, 79-5060
- Benzo(e)pyrene, 9,10-Dihydro-
 - Microsomes, Liver, 79-5060
- Benzo(e)pyrene, 4,4-Dihydro-4,5-dihydroxy-
 - Microsomes, Liver, 79-5060
- Benzo(e)pyrene, 9,10-Dihydro-9,10-dihydroxy-
 - Microsomes, Liver, 79-5060
- Benzo(g,h,i)perylene
 - Food Contamination, 79-5066
- Benzo(rst)pentaphene
 - S9-Fraction, 79-5059
- Cannabis
 - Mutagenic Activity, 79-5014
 - Smoke Condensate, 79-5014
- Carcinogen, Chemical
 - NADPH-Generating System, 79-4940
 - S9 Fraction, Review, 79-4803
- Coal Tar
 - Mutagenic Activity, 79-5067
 - Therapeutic Preparations, 79-5067
- Coronene
 - Food Contamination, 79-5066
- Dimethylamine, *N*-Nitroso-
 - Arabinose Resistance, 79-4988
- Fluoranthene
 - Food Contamination, 79-5066
- Gentamicin
 - Aminoglycosides, 79-5012
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Dose-Response Study, 79-5059
- Indeno(1,2,3-cd)pyrene
 - Food Contamination, 79-5066
- Kanamycin
 - Aminoglycosides, 79-5012
- Methanesulfonic Acid, Ethyl Ester
 - Dose-Response Study, 79-5059
- Mutagens
 - Ampicillin Resistance, Review, 79-4804
 - Fusarium moniliforme*, 79-5028
 - S9 Fraction, Review, 79-4804
- Propane, 1,2-Epoxy-
 - Mutagenic Activity, 79-4964
- Silver Sulfadiazine
 - Mutagenic Activity, 79-4954
- Sodium Azide

Ames Test (cont'd)

- Mutagenic Activity, 79-5005
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Aroclor 1254, 79-5078
 - Derivatives, 79-5078
 - Mutagenic Activity, 79-5078
- Toluene-2,4-diamine
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-5022
 - 5,6-Benzoflavone, 79-5022
- Triphenylene
 - Food Contamination, 79-5066
- Urea, 1-(1-Naphthyl)-2-thio-
 - Aroclor 1254, 79-4984
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-4984
 - Mutagenic Metabolite, 79-4984
- Zearalenone
 - Mutagenic Activity, 79-5029

Amino Acids

- DNA Repair
 - N*-Diazaoacetyl Derivatives, 79-4999
- Myeloma Proteins
 - Galactin-Binding Proteins, 79-5238
 - Immunoglobulins, Heavy Chain, 79-5238
- Plasmacytoma
 - Immunoglobulins, Heavy Chain, 79-5265
- Virus, Herpes Simplex 1
 - Peptide Chain Elongation, 79-5178

Amino Acyl T RNA Synthetases

- Methionine
 - Polycyclic Hydrocarbons, 79-5069

Aminoglycosides

- Gentamicin
 - Ames Test, 79-5012
- Kanamycin
 - Ames Test, 79-5012
- Saccharomyces cerevisiae*
 - Mutagenic Activity, 79-5012

Aminopyrine *N*-Demethylase

- Propane, 1,2-Epoxy-3,3,3-trichloro-
 - Microsomes, Liver, 79-4965

Ammonia

- Mycotoxins
 - Hepatotoxicity, 79-5031

Ammonium Sulfate

- Aniline, *N,N*-Dimethyl-
 - Mixed Function Oxidases, 79-4989
- Dimethylamine, *N*-Nitroso-
 - Metabolism, 79-4989
 - Mixed Function Oxidases, 79-4989
- Mixed Function Oxidases
 - Microsomes, Liver, 79-4989
- NADPH Cytochrome C Reductase
 - Microsomes, Liver, 79-4989
- 1-Naphthalenesulfonic Acid, 8-(Phenylamino)-
 - Mixed Function Oxidases, 79-4989

Androgens

- Hepatoma
 - Histological Study, Review, 79-4847
- Liver Diseases
 - Peliosis, Review, 79-4847
- Liver Neoplasms
 - Adenoma, 79-4847
 - Histological Study, Review, 79-4847
- Prostatic Neoplasms

drogens (cont'd)

Co-carcinogenic Effect, Review, 79-4929

-Androstan-3-one, 17 β -Hydroxy-

LS 1727

Metabolism, 79-5046

emia

Leukemia, Myelocytic

Precancerous Conditions, 79-5293

emia, Aplastic

Bone Marrow

Megakaryocytes, 79-5288

Chromosome Aberrations

Chromosomes, Human, 1-3, 79-5288

Thrombocytosis, 79-5288

Histocompatibility Antigens

Child, 79-5247

Parental Compatibility, 79-5247

Leukemia, Hairy Cell

Precancerous Conditions, Review, 79-4901

Leukemia, Myeloblastic

Precancerous Conditions, 79-5291

ngioma

Pancreatic Neoplasms

Hippel-Lindau Disease, 79-5303

ngiosarcoma

Benzenamine, 4,4'-Methylenebis(2-chloro)-

Dose-Response Study, Rat, 79-5024

Ethane, 1,2-Dichloro-

Carcinogenic Activity, Mouse, Rat, 79-4961

Ethylene, Chloro-

Carcinogenic Activity, Review, 79-4808

Ethylene, Chloro- Polymer

Occupational Hazard, Review, 79-4808

Splenic Neoplasms

12-*O*-Tetradecanoylphorbol-13-acetate, 79-5041

Thyroid Neoplasms

12-*O*-Tetradecanoylphorbol-13-acetate, 79-5041

Aniline

Water Pollution

Derivatives, 79-5020

Quantitation Method, 79-5020

Aniline, *N,N*-Dimethyl-

Ammonium Sulfate

Mixed Function Oxidases, 79-4989

Aniline, *N,N*-Dimethyl-*p*-phenylazo-

Carrier Proteins

Cell Membrane, 79-4985

Glutathione

Metabolism, Rat, 79-5021

Liver Neoplasms

Antigens, Neoplasm, 79-4907

Fetal Globulins, 79-4907

Immune Response, Review, 79-4907

Phosphatidylcholines

Membranes, Binding, 79-4985

Aniline, *N*-Methyl-(*p*-phenylazo)-

Glutathione Adducts

Biliary Metabolites, 79-5021

1-Anthracenamine

Arylnitrenium Ions

Mutagenic Activity, 79-5038

2-Anthracenamine

Arylnitrenium Ions

Mutagenic Activity, 79-5038

Anthracene

Diol Epoxides

Electronic Structures, 79-5037

Anti-Antibodies

Virus, Herpes Simplex 1

IgG, 79-5183

Interferon, 79-5173

Pyruvate Kinase, 79-5183

Antibodies

Virus, Herpes Simplex 2

Hypersensitivity, Delayed, 79-5194

Antibodies, Viral

Burkitt's Lymphoma

Virus, Epstein-Barr, 79-5166, 79-5167

Cervix Neoplasms

Carcinoma In Situ, 79-5175

Virus, Cytomegalo, 79-5175

Virus, Herpes Simplex, 79-5175

Epidermodysplasia Verruciformis

Virus, Papilloma, 79-5172

Head and Neck Neoplasms

Virus, Epstein-Barr, 79-5166

Infectious Mononucleosis

Virus, Epstein-Barr, 79-5166

Nasopharyngeal Neoplasms

Virus, Epstein-Barr, 79-5166, 79-5167

Virus, Cytomegalo

Pregnancy, 79-5175

Virus, Epstein-Barr

Hypersensitivity, Delayed, 79-5167

Virus, Herpes Simplex

Pregnancy, 79-5175

Virus, Measles

Cell Membrane, 79-5228

Hemolysins, 79-5228

Phosphoproteins, 79-5228

Antibody Formation

Virus, Friend Murine Leukemia

Methanesulfonic Acid, Methyl Ester, 79-4952

Virus, Herpes

Immune Response, Review, 79-4875

Virus, Herpes Lucke

IgG, 79-5126

Antibody Specificity

Melanoma

Antigens, Neoplasm, 79-5263

Hybrid Cells, 79-5263

Virus, Herpes Simplex 1

Deoxyribonuclease, 79-5191

Thymidine Kinase, 79-5191

Virus, Herpes Simplex 2

Deoxyribonuclease, 79-5191

Thymidine Kinase, 79-5191

Antigen-Antibody Complex

Burkitt's Lymphoma

IgG, 79-5165

Neoplasm Recurrence, 79-5165

Virus, Epstein-Barr, 79-5165

Colonic Neoplasms

Cytotoxins, 79-5239

IgG, 79-5239

Antigen-Antibody Complex (cont'd)

- Dysgammaglobulinemia
 - Casein, 79-5240
- Immunologic Deficiency Syndromes
 - IgA, 79-5240
 - Milk Proteins, 79-5240
- Melanoma
 - Cytotoxins, 79-5239
 - IgG, 79-5239
- Virus, Epstein-Barr
 - Immune Response, Review, 79-4890

Antigen-Antibody Reactions

- Cholanthrene, 3-Methyl-
 - Immunization, 79-5054
- Gastrointestinal Neoplasms
 - Virus, Herpes Simplex, 79-5191
- Hodgkin's Disease
 - Virus, Herpes Simplex, 79-5191
- Leukemia, Myelocytic
 - Virus, Herpes Simplex, 79-5191
- Lung Neoplasms
 - Virus, Herpes Simplex, 79-5191
- Lymphoma
 - Histocompatibility Antigens, 79-5270
- Neoplasms, Experimental
 - Cholanthrene, 3-Methyl-, 79-5054
- Prostatic Neoplasms
 - Virus, Herpes Simplex, 79-5191
- Sarcoma, Mast Cell
 - Immunosuppression, 79-5273
 - Neoplasm Transplantation, 79-5273
- Virus, Feline Leukemia
 - Antigenic Determinants, 79-5152
- Virus, Feline Sarcoma
 - Antigenic Determinants, 79-5152
- Virus, Herpes
 - Immune Response, Review, 79-4877

Antigenic Determinants

- Bladder Neoplasms
 - Benzoic Acid, 2-Amino-3-oxy-, 79-5253
 - Immunity, Cellular, 79-4992
- Hypersensitivity, Delayed
 - Histocompatibility Antigens, 79-5245
- Melanoma
 - Beta 2 Microglobulin, 79-5276
 - Histocompatibility Antigens, 79-5276
- Virus, Avian Leukosis-Sarcoma
 - Virus, Rous-Associated, 79-5118
- Virus, Epstein-Barr
 - Primate Viruses, Review, 79-4879
- Virus, Feline Leukemia
 - Antigen-Antibody Reactions, 79-5152
- Virus, Feline Sarcoma
 - Antigen-Antibody Reactions, 79-5152
 - Virus, Feline Leukemia, 79-5152
- Virus, Friend Spleen Focus-Forming
 - Glycoproteins, 79-5131
 - Virus, Mink Cell Focus-Inducing, 79-5131
- Virus, Gazdar Murine Sarcoma
 - Radioimmunoassay, 79-5139
 - Virus, Helper, 79-5139
- Virus, Gross Murine Sarcoma
 - Virus, Helper, 79-5139
- Virus, Hamster C-Type RNA Tumor
 - Peptides, 79-5148
- Virus, Herpes

Antigenic Determinants (cont'd)

- Isolation and Characterization, Review, 79-4876
- Virus, Mink Cell Focus-Inducing
 - Glycoproteins, 79-5131
 - Membrane Proteins, 79-5145
- Virus, Moloney Murine Sarcoma
 - Virus, Helper, 79-5139
- Virus, Murine Leukemia
 - Membrane Proteins, 79-5145
 - Virus, Mink Cell Focus-Inducing, 79-5145
- Virus, Rous Sarcoma
 - Glycoproteins, 79-5116
 - Virus, Rous-Associated, 79-5118

Antigens

- RNA
 - Immunity, Cellular, 79-5234
- Virus, Marek's Disease Herpes
 - Immunity, Cellular, 79-5122

Antigens, Neoplasm

- Liver Neoplasms
 - Aniline, *N,N*-Dimethyl-*p*-phenylazo-, 79-4907
- Mammary Neoplasms, Experimental
 - Hybrid Cells, 79-5279
- Melanoma
 - Antibody Specificity, 79-5263
 - Cell Membrane, 79-5276
 - Isolation and Characterization, 79-5276
- Neuroblastoma
 - Lymphocyte Transformation, 79-5255
- Teratoid Tumor
 - Glycolipids, 79-5262
 - Glycoproteins, 79-5262
 - Immunoprecipitation, 79-5262
- Virus, Adeno 2 - SV40 Hybrid
 - RNA, Messenger, 79-5199
- Virus, SV40
 - Cell Cycle Kinetics, 79-5216
 - Deletion Mutants, 79-5214
 - DNA Replication, 79-5216
 - Interferon, 79-5217
 - Nucleotide Sequence, 79-5212, 79-5213
 - RNA, Messenger, 79-5211, 79-5214
 - Virus, Helper, 79-5215

Antigens, Viral

- Breast Neoplasms
 - Precancerous Conditions, 79-5226
 - Virus, D-Type RNA Tumor, 79-5226
- Hodgkin's Disease
 - Virus, Epstein-Barr, 79-5171
- Infectious Mononucleosis
 - Virus, Epstein-Barr, 79-5171
- Lymphoma
 - Virus, Epstein-Barr, 79-5171
- Tonsillitis
 - Virus, Epstein-Barr, 79-5171
- Virus, Epstein-Barr
 - Latent Infections, Review, 79-4878
 - Lymphocyte Transformation, 79-5161
 - B-Lymphocytes, 79-5171
- Virus, Herpes Lucke
 - Latent Infections, Review, 79-4878
- Virus, Herpes Simplex 1
 - HEP-2-Cells, Isolation and Characterization 79-5190
- Virus, Herpes Simplex 2
 - HEP-2-Cells, Isolation and Characterization

Antigens, Viral (cont'd)

- HEP-2-Cells, Isolation and Characterization 79-5190
- Virus, Marek's Disease Herpes
 - B-Lymphocytes, 79-5124
 - T-Lymphocytes, 79-5124
- Virus, Varicella-Zoster
 - Lymphocyte Transformation, 79-5159

Antilymphocyte Serum

- T-Lymphocytes
 - Suppressor Cells, Review, 79-4903
- Papilloma
 - Immunosuppression, 79-5256
 - T-Lymphocytes, 79-5256
- Skin Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5256
- Virus, Cytomegalo
 - Virus Activation, 79-5158

Antineoplastic Agents

- Ames Test
 - Mutagenic Metabolite, 79-5090
- Escherichia coli*
 - Mutagenic Metabolite, 79-5090
- Urine
 - Mutagenic Metabolite, 79-5090

Aroclor 1254

- Benzo(e)pyrene
 - Ames Test, 79-5060
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Ames Test, 79-5078
- Urea, 1-(1-Naphthyl)-2-thio-
 - Ames Test, 79-4984

Arsenic

- Air Pollution
 - Canada, Review, 79-4812
- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813

Aryl Hydrocarbon Hydroxylases

- Actinomycin D
 - Enzyme Induction, Review, 79-4839
- Adrenal Cortex
 - 7,8-Benzoflavone, 79-5073
 - Cholanthrene, 3-Methyl-, 79-5073
 - Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 79-5073
- Benzo(a)pyrene
 - p*-Cresol, 2,6-Di-*tert*-butyl-, 79-5074
 - Genetics, Mouse, Review, 79-4840
 - Lung, Mouse, 79-5025
 - Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-5074
- 5,6-Benzoflavone
 - Lung, Mouse, 79-5025
- Carcinogen, Chemical
 - Enzyme Activation, Review, 79-4840
- Cholanthrene, 3-Methyl-
 - Genetics, Mouse, Review, 79-4840
 - Lung, Mouse, 79-5025
 - Tissue Distribution, Rat, 79-5074
- Cholesterol
 - Tissue Distribution, Rat, 79-5074
- Chromosomes, Human, 1-3
 - Hybrid Cells, Review, 79-4839
- Corticotropin
 - Adrenal Cortex, Rat, 79-5073
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Liver, Intestines, 79-5095

Aryl Hydrocarbon Hydroxylases (cont'd)

- Estradiol
 - Tissue Distribution, Rat, 79-5074
- Estrone
 - Tissue Distribution, Rat, 79-5074
- Ethyl Alcohol
 - Microsomes, Liver, 79-4956
- Fibrosarcoma
 - Radiation, Ionizing, 79-5100
- Lymphocytes
 - Twins, Review, 79-4839
- Neoplasms, Experimental
 - Genetics, Mouse, Review, 79-4840
- Polycyclic Hydrocarbons
 - Enzyme Induction, Review, 79-4839
- Propane, 1,2-Epoxy-3,3,3-trichloro-
 - Microsomes, Liver, 79-4965
- Radiation, Ionizing
 - Benz(a)anthracene, 79-5100
 - Cells, Cultured, 79-5100
 - Lung, Mouse, 79-5025
- RNA Replication
 - Enzyme Induction, Review, 79-4839
- Skin Neoplasms
 - Psoriasis, 79-5277

Asbestos

- Adenocarcinoma
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester 79-4978
- Air Pollution
 - Canada, Review, 79-4812
- Benzo(a)pyrene
 - Adsorption, Review, 79-4810
- Blood Vessels
 - Fiber Transport, Mouse, 79-4942
- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 - Co-carcinogenic Effect, 79-4978
- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813
- Environmental Hazard
 - Epidemiology, Review, 79-4811
- Lung Neoplasms
 - Occupational Hazard, 79-5369
- Mesothelioma
 - Epidemiology, Review, 79-4815
- Mesothelium
 - Ultrastructural Study, Milk Spots, 79-4942
- Myosarcoma
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester 79-4978
- Respiratory Tract Neoplasms
 - Mesothelioma, 79-4978
- Sarcoma
 - Ultrastructural Study, Milk Spots, 79-4943
 - Virus, Moloney Murine Leukemia, 79-4943
- Smoking
 - Co-carcinogenic Effect, 79-5369
 - Co-carcinogenic Effect, Review, 79-4815, 79-4830
- Virus, Moloney Murine Leukemia
 - Co-carcinogenic Effect, 79-4943

Asbestosis

- Occupational Hazard
 - Epidemiology, Germany, 79-4854

Ascorbic Acid

- Copper
 - Metabolism, Review, 79-4844

- Ascorbic Acid (cont'd)**
 Free Radicals
 Metabolism, Review, 79-4844
 Lead
 Metabolism, Review, 79-4844
 Selenium
 Metabolism, Review, 79-4844
 Zinc
 Metabolism, Review, 79-4844
- Astrocytoma**
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 DNA Repair, 79-5200
 Isoproterenol
 Adenosine Cyclic 3',5' Monophosphate, 79-5072
 Adenyl Cyclase, 79-5072
 Receptors, Adrenergic, 79-5072
 Prostaglandins E
 Adenosine Cyclic 3',5' Monophosphate, 79-5072
 Adenyl Cyclase, 79-5072
 Virus, Adeno 5
 Virus Activation, 79-5200
- Ataxia Telangiectasia**
 Bleomycin
 DNA Repair, 79-5091
- Autoantibodies**
 Neoplasms, Experimental
 Complement Fixation Tests, 79-5274
 IgM, 79-5274
 Transplantation Immunology, 79-5274
- Autoimmune Diseases**
 Leukemia, Lymphoblastic
 Genetics, 79-5267
 Hyperthyroidism, 79-5267
 Rheumatic Fever, 79-5267
 Leukemia, Myeloblastic
 Genetics, 79-5267
- Avian Leukosis**
 Virus, Marek's Disease Herpes
 B-Lymphocytes, 79-5124
- Azacytidine**
 see *s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-
- Azaserine**
 see Serine, Diazoacetate (Ester)
- Azathioprine**
 Erythroleukemia
 Case Report, Kidney Transplant, 79-5042
 Chromosome Abnormalities, 79-5042
- 6-Azaauridine**
 see *as*-Triazine-3,5-(2*H*,4*H*)-dione, 2- β -*D*-Ribofuranosyl-
- Bacillus subtilis***
 Zearalenone
 DNA, Bacterial, 79-5029
 Mutagenic Activity, 79-5029
- Bacillus thuringiensis***
 Endotoxins
 Mutagenic Activity, Plants, 79-5027
 Zearalenone
 Mutagenic Activity, 79-5029
- Bacteria**
 Aflatoxin B1
 Phagocytosis, 79-5033
- Bacteria (cont'd)**
 Bile Acids and Salts
 Co-carcinogenic Activity, Review, 79-4930
 Intestinal Neoplasms
 Co-carcinogenic Effect, Review, 79-4918
- Bacteriophages**
 Virus, Polyoma
 DNA, Viral, 79-5208
- Barbituric Acid, 5-Ethyl-5-phenyl-**
 Benzo(a)pyrene
 Adenosine Triphosphatase, 79-5064
 Benzo(a)pyrene 4,5-Oxide
 Nucleoside Adducts, 79-5063
 1,3-Butadiene, 2-Chloro-
 Mutagenic Activity, 79-4959
 Demethylases
 Metabolism, Liver, 79-4958
 Diethylamine, *N*-Nitroso-
 Nucleic Acids, 79-4990
 Ethylene, Chloro-
 Mutagenic Activity, 79-4959
 Ethylene, 1,1-Dichloro-
 Mutagenic Activity, 79-4959
 Hepatoma
 DNA Replication, 79-5057
 Liver Neoplasms
 Co-carcinogenic Activity, Review, 79-4836
 Microsomes, Liver
 DNA Replication, 79-5057
 Propane, 1,2-Epoxy-3,3,3-trichloro-
 Oxygenases, 79-4965
 Toluene-2,4-diamine
 Ames Test, 79-5022
 Urea, 1-(1-Naphthyl)-2-thio-
 Ames Test, 79-4984
- Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt**
 Dieldrin
 Epoxide Hydratases, 79-5068
 Oxygenases, 79-5068
- BCG Vaccination**
 Carcinoma, Basal Cell
 Case Report, 79-5105
 Cicatrix, 79-5105
- Benz(a)anthracene**
 Radiation, Ionizing
 Aryl Hydrocarbon Hydroxylases, 79-5100
- Benz(a)anthracene, 7,12-Dimethyl-**
 Abnormalities
 Ovary, Testis, Mouse, 79-5050
 Acetic Acid, (Ethylenedinitrilo)tetra-
 DNA, Binding, 79-5044
 Age Factors
 Carcinogenic Metabolite, 79-5058
 Carcinoma, Epidermoid
 Lipids, 79-5052
 DNA
 Cell Cycle Kinetics, 79-5044
 Epidermal Cells
 DNA, Binding, 79-5044
 Fibroblasts
 Carcinogenic Metabolite, 79-5058
 Gonadotropins
 Serum Levels, 79-5050
 Keratoacanthoma

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)
 Neoplasm Regression, Spontaneous, 79-5045
 Leukemia, Myelocytic
 Rat, Germfree, Review, 79-4918

LH
 Serum Levels, 79-5050

Lipids
 Metabolism, Rat, 79-5048

Mammæ
 Body Burden, Rat, 79-5048

Mammary Neoplasms, Experimental
 Adenocarcinoma, 79-4918
 Histological Study, Rat, 79-5049
 Hydroxylamine, 79-5049
 LS 1727, 79-5046
 Norgestrel, 79-5046
 Rat, Germfree, Review, 79-4918
 Receptors, Hormone, 79-5047
 Urea, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitroso-
 79-5046

Pancreatic Neoplasms
 Carcinogenic Potential, 79-5373

Papilloma
 Lipids, 79-5052

Sarcoma
 Lipids, 79-5052

Skin Neoplasms
 Antilymphocyte Serum, 79-5256
 Lipids, 79-5052
 12-O-Tetradecanoylphorbol-13-acetate, 79-5256

Sterility
 Prenatal Exposure, Mouse, 79-5050

Uterine Neoplasms
 Adenocarcinoma, 79-5051
 Carcinoma, Epidermoid, 79-5051
 Ovariectomy, Hypophysectomy, 79-5051
 Precancerous Conditions, 79-5051

Benz(e)acephenanthrylene
 Ames Test
 Food Contamination, 79-5066
 Water Pollution
 Quantitation Method, 79-5056

Benzaldehyde
 Nitrosamines
 Fragmentation Products, Review, 79-4823

Benzenamine, 4,4'-Methylenebis(2-chloro)-
 Adenocarcinoma
 Dose-Response Study, Rat, 79-5024
 Angiosarcoma
 Dose-Response Study, Rat, 79-5024
 Hepatoma
 Dose-Response Study, Rat, 79-5024
 Lung Neoplasms
 Adenocarcinoma, 79-5024
 Adenoma, 79-5024
 Dietary Proteins, 79-5024
 Dose-Response Study, Rat, 79-5024
 Mammary Neoplasms, Experimental
 Adenocarcinoma, 79-5024

Benzene
 Carcinogen, Chemical
 Occupational Hazard, Review, 79-4813
 Cyclohexene Oxide
 Phosphodiester, 79-4968
 Leukemia

Benzene (cont'd)
 Occupational Hazard, 79-5358
 Leukemia, Monocytic
 Occupational Hazard, 79-5358
 Leukemia, Myelocytic
 Occupational Hazard, 79-5358
 Transplacental Carcinogenesis
 Epidemiology, Review, 79-4815

Benzene, 4-Allyl-1,2-(methylenedioxy)-
 Liver Neoplasms
 Carcinoma, 79-5023
 Stomach Neoplasms
 Carcinogenic Potential, Mouse, 79-5023

Benzene, 4-Azido-1,3-dinitro-
 Ames Test
 Dose-Response Study, 79-5005
Escherichia coli
 Mutagenic Activity, 79-5005

Benzene, 4-Azido-1-Fluoro-2-nitro-
 Ames Test
 Dose-Response Study, 79-5005
Escherichia coli
 Mutagenic Activity, 79-5005

Benzene, 1,2-(Methylenedioxy)-4-propenyl-
 Stomach Neoplasms
 Carcinogenic Potential, Mouse, 79-5023

Benzene, 1,2-(Methylenedioxy)-4-propyl-
 Liver Neoplasms
 Carcinoma, 79-5023
 Stomach Neoplasms
 Carcinoma, 79-5023
 Hyperplasia, 79-5023

1,3-Benzenedicarbonitrile, 2,4,5,6-Tetrachloro-
 Chromosome Aberrations
Hordeum vulgare, 79-4972

Benzidine
 Pancreatic Neoplasms
 Occupational Hazard, 79-5373

1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 Bladder Neoplasms
 Co-carcinogenic Effect, Review, 79-4864

Benzo(a)pyren-9-ol 4,5-Oxide
 Microsomes, Liver
 DNA Adducts, 79-5062

Benzo(a)pyrene
 Adenosine Triphosphatase
 Hepatocarcinogenesis, 79-5064
 Age Factors
 Carcinogenic Metabolite, 79-5058
 Air Pollution
 Spectrum Analysis, 79-5055
 Ames Test
 S9-Fraction, 79-5059
 Aryl Hydrocarbon Hydroxylases
 Genetics, Mouse, Review, 79-4840
 Lung, Mouse, 79-5025
 Asbestos
 Adsorption, Review, 79-4810
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Adenosine Triphosphatase, 79-5064
 Caffeine
 DNA Replication, 79-5057

- Benzo(a)pyrene (cont'd)**
 Carcinogenic Metabolite
 Quantum Mechanics, Review, 79-4915
 Structure-Activity Relationship, Review, 79-4802
 Carcinoma, Epidermoid
 Lipids, 79-5052
 Cells, Cultured
 DNA, Binding, 79-5085
p-Cresol, 2,6-Di-*tert*-butyl-
 Aryl Hydrocarbon Hydroxylases, 79-5074
 Cytochrome P-450
 Metabolism, Review, 79-4840
 Diol Epoxides
 Electronic Structures, 79-5037
 DNA
 Carcinogenic Metabolite, Review, 79-4838
 Ethyl Alcohol
 DNA, Binding, 79-4956
 Fibroblasts
 Carcinogenic Metabolite, 79-5058
 DNA, Binding, 79-5061
 Hepatoma
 DNA Replication, 79-5057
 Liver
 DNA, Binding, 79-5061
 Liver Neoplasms
 Hepatectomy, 79-5064
 Lung Neoplasms
 Sarcoma, 79-5018
 Microsomes
 DNA, Binding, 79-5085
 Microsomes, Liver
 DNA Adducts, 79-5062
 DNA, Binding, 79-5061
 DNA Replication, 79-5057
 Mutagenic Activity
 Mammals, Microorganisms, Review, 79-4835
 Nucleoside Adducts
 Liver, Lung, Rat, 79-5063
 Papilloma
 Lipids, 79-5052
 Phenol, (1,1-Dimethylethyl)-4-methoxy-
 Aryl Hydrocarbon Hydroxylases, 79-5074
 Phosphodiester
 Diol Epoxides, 79-4968
 Respiratory Tract Neoplasms
 Agar, 79-4947
 Air Pollution, 79-5366
 Iron Oxide, 79-4947
 Manganese Dioxide, 79-4947
 Silica, 79-4947
 Silica
 Adsorption, Review, 79-4810
 Skin Neoplasms
 Lipids, 79-5052
 Water Pollution
 Quantitation Method, 79-5056
- Benzo(a)pyrene, 6-Acetoxy-methyl-**
 Adenine Nucleotides
 Carcinogenic Metabolite, 79-5065
 Adenosine Triphosphate
 DNA, Binding, 79-5065
 Microsomes, Liver
 DNA, Binding, 79-5065
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-5,6-Benzoflavone**
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-(cont'd)**
 Nucleoside Adducts, 79-5063
 Cholanthrene, 3-Methyl-
 Nucleoside Adducts, 79-5063
 Microsomes, Liver
 DNA Adducts, 79-5062
- Benzo(a)pyrene-6-methanol**
 Adenine Nucleotides
 Carcinogenic Metabolite, 79-5065
 Adenosine Triphosphate
 DNA, Binding, 79-5065
 Cholanthrene, 3-Methyl-
 DNA, Binding, 79-5065
 Microsomes, Liver
 Cholanthrene, 3-Methyl-, 79-5065
- Benzo(a)pyrene 4,5-Oxide**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Nucleoside Adducts, 79-5063
 Microsomes, Liver
 DNA Adducts, 79-5062
- Benzo(b)fluoranthrene**
 see Benz(e)acephenanthrylene
- Benzo(e)pyrene**
 Aroclor 1254
 Ames Test, 79-5060
 Microsomes, Liver
 Ames Test, 79-5060
 Mutagenic Activity
 Bay Region Epoxide, 79-5060
- Benzo(e)pyrene, 9,10-Dihydro-**
 Microsomes, Liver
 Ames Test, 79-5060
 Mutagenic Activity
 Bay Region Epoxide, 79-5060
- Benzo(e)pyrene, 4,4-Dihydro-4,5-dihydroxy-**
 Microsomes, Liver
 Ames Test, 79-5060
- Benzo(e)pyrene, 9,10-Dihydro-9,10-dihydroxy-**
 Microsomes, Liver
 Ames Test, 79-5060
- Benzo(g,h,i)perylene**
 Ames Test
 Food Contamination, 79-5066
 Water Pollution
 Quantitation Method, 79-5056
- Benzo(k)fluoranthene**
 Water Pollution
 Quantitation Method, 79-5056
- Benzo(rst)pentaphene**
 Ames Test
 S9-Fraction, 79-5059
- 2H-1,4-Benzodiazepin-2-one, 1,3-Dihydro-7-nitro-5-phenyl-**
 Ethyl Alcohol
 Amino Derivatives, 79-5004
 Metabolism, Liver, 79-5004
- 5,6-Benzoflavone**
 Aryl Hydrocarbon Hydroxylases
 Lung, Mouse, 79-5025
 Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-

5,6-Benzoflavone (cont'd)
 Nucleoside Adducts, 79-5063
 Toluene-2,4-diamine
 Ames Test, 79-5022

7,8-Benzoflavone
 Adrenal Cortex
 Aryl Hydrocarbon Hydroxylases, 79-5073

Benzoic Acid, 2-Amino-3-oxy-
 Bladder Neoplasms
 Antigenic Determinants, 79-5253
 Urine, 79-5253

Benzoic Acid, *p*-Hydroxymercuri-
 Glucose, 2-Deoxy-
 Metabolism, 79-5077

Benzoic Acid, *p*-Nitro-
 Ethyl Alcohol
 Alcohol Oxidoreductases, 79-5004
 Metabolism, Liver, 79-5004

***p*-Benzoquinone, 2,3,5-Tris(1-aziridinyl)-**
 Neoplasms
 Drug Therapy, Review, 79-4834

***p*-Benzoquinone, 2,3,5-Tris(1-aziridinyl)-**
 Mutagenic Activity
 Mammals, Microorganisms, Review, 79-4835

Benzylamine, *N*-Butyl-*N*-nitroso-
 Nitrosamines
 Fragmentation Products, Review, 79-4823

Beta 2 Microglobulin
 Melanoma
 Antigenic Determinants, 79-5276

Bile Acids and Salts
 Bacteria
 Co-carcinogenic Activity, Review, 79-4930

Bile Duct Neoplasms
 Myoblastoma
 Blacks, 79-5329
 Case Report, 79-5329
 Cholecystitis, 79-5329

1,1'-Biphenyl, 2,2',4,4'-Tetrachloro-
 Propane, 1,2-Epoxy-3,3,3-trichloro-
 Binding, 79-4965

Bladder Neoplasms
 Adenocarcinoma
 Precancerous Conditions, 79-5341
 Antigenic Determinants
 Immunity, Cellular, 79-4992
 1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 Co-carcinogenic Effect, Review, 79-4864
 Benzoic Acid, 2-Amino-3-oxy-
 Antigenic Determinants, 79-5253
 Urine, 79-5253
 1-Butanol, 4-(Butylnitrosamino)-
 Histocompatibility Antigens, 79-4992
 Carcinogen, Chemical
 Glucuronidase, 79-4846
 13-*cis*-Retinoic Acid, 79-4846
 Carcinogen, Environmental
 Glucuronidase, 79-4846
 Carcinoma
 Acetamide, *N*-Fluoren-2-yl-, 79-4864
 1-Butanol, 4-(Butylnitrosamino)-, 79-4864

Bladder Neoplasms (cont'd)
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 79-4864
 2-Naphthylamine, 79-4864
 Urea, Methyl Nitroso-, 79-4864
 Carcinoma, Epidermoid
 Precancerous Conditions, 79-5341
 Carcinoma In Situ
 Neoplasm Metastasis, Review, 79-4914
 Carcinoma, Papillary
 Animal Model, Rat, 79-4993
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 79-4993
 Carcinoma, Transitional Cell
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 79-4993
 Precancerous Conditions, 79-5341
 Cell Membrane
 Neoplasm Metastasis, Review, 79-4914
 Cyclohexanesulfonic Acid, Monosodium Salt
 Co-carcinogenic Effect, Review, 79-4864
 Cyclophosphamide
 Epidemiology, Review, 79-4817
 Epithelium
 Neoplasm Seeding, Review, 79-4914
 Ethylene, Trichloro-
 Occupational Hazard, 79-5376
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 Neoplasm Metastasis, 79-4993
 Glucuronidase
 Cell Division, 79-4846
 Histocompatibility Antigens
 Transplantation Immunology, 79-4992
 2-Imidazolidinethione
 Carcinogenic Potential, Review, 79-4833
 Precancerous Conditions
 Histological Study, Mouse, 79-5341
 Retinoic Acid
 Cell Differentiation, 79-5395
 Cell Migration Inhibition, 79-5395
 DNA Replication, 79-5395
 Keratin, 79-5395
 Smoking
 Epidemiology, 79-5389
 Tars
 Tobacco, 79-5389
 Tryptophan
 Co-carcinogenic Effect, Review, 79-4864

Bleomycin
 Ataxia Telangiectasia
 DNA Repair, 79-5091

Blood-Brain Barrier
 Quinoline, 4-(Hydroxyamino)-, 1-Oxide
 Biological Transport, Mouse, 79-5007
 Quinoline, 4-Nitro-, 1-Oxide
 Biological Transport, Mouse, 79-5007

Blood Groups
 Carcinoma, Transitional Cell
 Phenotype, 79-5283

Blood Vessels
 Asbestos
 Fiber Transport, Mouse, 79-4942

Bone and Bones
 Americium
 Body Burden, 79-5106

Bone Marrow

- Anemia, Aplastic
 - Megakaryocytes, 79-5288
- Cyclophosphamide
 - Chromosome Aberrations, 79-5079
- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-
 - Chromosome Aberrations, 79-4960
- Graft vs Host Reaction
 - Eosinophils, 79-5296
 - Macrophages, 79-5296
- Graft Rejection
 - Immune Response, Mouse, 79-5182
- Hematological Diseases
 - Eosinophils, 79-5296
 - Macrophages, 79-5296
- Leukemia, Myeloblastic
 - Eosinophils, 79-5296
 - Macrophages, 79-5296
 - Precancerous Conditions, 79-5291
- Leukemia, Myelocytic
 - Cell Abnormalities, 79-5293
- Nitrogen Monoxide
 - Chromosome Aberrations, 79-4960
- Propane, 1,2-Epoxy-
 - Lymphocytes, 79-4964
- 4,4'-Stilbenediol, α,α' -Diethyl-, Bis(dihydrogen phosphate)
 - Chromosome Aberrations, 79-5079
- Virus, Avian Reticuloendotheliosis
 - Cell Transformation, Neoplastic, 79-5120

Bone Marrow Diseases

- Valine, 3-Mercapto-
 - Toxicity, Review, 79-4834

Bone Neoplasms

- Chondroma
 - Ethylene, Chloro-, 79-4808

Bone Resorption

- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Calcium, 79-5082

Bracken Fern

- Intestinal Neoplasms
 - Adenocarcinoma, 79-5035

Brain

- Hepatoma
 - Neoplasm Metastasis, 79-5109

Brain Diseases, Metabolic

- Copper
 - Proteins, Kidney, 79-4945
 - Tissue Distribution, Mouse, 79-4945

Brain Neoplasms

- Acromegaly
 - Radiotherapy, 79-5102
- Adenoma
 - Neoplasm Metastasis, 79-5298
- Diet
 - Restriction, 79-5397
- Ethnic Groups
 - Epidemiology, Child, 79-5357
- Ethyl Alcohol
 - Epidemiology, 79-5356
- Fibrosarcoma
 - Radiation, Ionizing, 79-5102
- Meningioma
 - Case Report, Psychiatric Symptoms, 79-5310

Brain Neoplasms (cont'd)

- Radiation, Ionizing
 - Case Report, 79-5102
- Ultraviolet Rays
 - DNA Repair, 79-5200
- Urea, Ethyl Nitroso-
 - Ultrastructural Study, Rat, 79-4980
- Virus, Adeno 5
 - DNA Repair, 79-5200
- Wounds and Injuries
 - Neoplasm Metastasis, 79-5109

Bravo

- see 1,3-Benzenedicarbonitrile, 2,4,5,6-Tetrachloro-

Breast Neoplasms

- Antigens, Viral
 - Precancerous Conditions, 79-5226
- Carcinoembryonic Antigen
 - Ascites, Pleural Effusions, 79-5242
- Concanavalin A
 - Lymphocyte Transformation, 79-5254
- Contraceptives, Oral
 - Epidemiology, Review, 79-4931
- Diet
 - Epidemiology, Review, 79-4930
- Dietary Fats
 - Epidemiology, Review, 79-4927, 79-4928
- Digitalis
 - Receptors, Estrogen, Review, 79-4848
- Digoxin
 - Receptors, Estrogen, Review, 79-4848
- Estrogenic Substances, Conjugated
 - Epidemiology, 79-5354
- Estrogens
 - Menopause, Review, 79-4928
 - Risk Factors, Review, 79-4851
- Neoplasms, Multiple Primary
 - Epidemiology, 79-5355
- Plant Agglutinins
 - Lymphocyte Transformation, 79-5254
- Pregnancy
 - Epidemiology, 79-5360
 - Epidemiology, Review, 79-4939
 - Immunosuppression, 79-5360
- Prolactin
 - Menopause, Review, 79-4928
- Radiation, Ionizing
 - Epidemiology, Review, 79-4815
- Reserpine
 - Carcinogenic Potential, Review, 79-4849
- Virus, D-Type RNA Tumor
 - Antigens, Viral, 79-5226
- Virus, RNA Tumor
 - Carcinogenic Potential, Review, 79-4888

Brenner Tumor

- Ovarian Neoplasms
 - Epidemiology, 79-5380

Bronchial Neoplasms

- Burns, Inhalation
 - Case Report, 79-5108
- Polyps
 - Burns, Inhalation, 79-5108
- Smoking
 - Precancerous Conditions, Review, 79-4845

Bronchitis

- Chromium

Bronchitis (cont'd)

Occupational Hazard, 79-4946

Burkitt's Lymphoma

Antigen-Antibody Complex

Neoplasm Recurrence, 79-5165

Cells, Cultured

Tumorigenicity, Review, 79-4891

Concanavalin A

Binding Sites, Review, 79-4905

IgG

Antigen-Antibody Complex, 79-5165

Lymphocytes

Immunologic Capping, Review, 79-4905

Virus, Epstein-Barr

Antibodies, Viral, 79-5166, 79-5167

Antigen-Antibody Complex, 79-5165

Epidemiology, Review, 79-4894

Hypersensitivity, Delayed, 79-5167

Molecular Biology, Review, 79-4896

Burns

Carcinoma, Epidermoid

Cicatrix, Review, 79-4860

Keratoacanthoma

Cicatrix, Review, 79-4860

1,3-Butadiene, 2-Chloro-

Barbituric Acid, 5-Ethyl-5-phenyl-

Mutagenic Activity, 79-4959

Cells, Cultured

Cell Transformation, Neoplastic, 79-4967

Lung Neoplasms

Fibrosarcoma, 79-4967

1-Butanol, 4-(Butylnitrosamino)-

Bladder Neoplasms

Carcinoma, 79-4864

Histocompatibility Antigens, 79-4992

Butyric Acid, 4-(*p*-Bis(2-chloroethyl)aminophenyl)-

Chromatids

Chromosome Aberrations, 79-4994

Butyric Acid, 4-Bromo-, Ethyl Ester

4,4'-Stilbenediol, α,α' -Diethyl-

Carboxypropyl Derivative, 79-5081

Butyric Acid, Sodium Salt

Cholera Toxin

Binding Sites, 79-4966

Erythroleukemia

Gangliosides, 79-4966

Cachexia

Kidney Neoplasms

Animal Model, Mouse, 79-5280

Immunosuppression, 79-5280

Cadmium

Tobacco

Heavy Metal Levels, 79-4944

Risk Factors, 79-4944

Caffeine

Mutagenic Activity

Mammals, Microorganisms, Review, 79-4835

Calcitonin

Thyroid Neoplasms

Hyperplasia, 79-5300

Calcium

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Metabolism, Rat, 79-5095

D-Gluconic Acid, Strontium Salt

Serum Levels, 79-4951

Phosphatidylinositols

Metabolism, Review, 79-4835

4,4'-Stilbenediol, α,α' -Diethyl-

Alkaline Phosphatase, 79-5082

Bone Resorption, 79-5082

Proline, 4-Hydroxy-, 79-5082

Cannabis

Ames Test

Mutagenic Activity, 79-5014

Smoke Condensate

Ames Test, 79-5014

Cantharidin

DNA Replication

Cell Cycle Kinetics, 79-4973

Epidermis, Mouse, 79-4973

Carbamic Acid, *N*-Butyl-*N*-nitroso-

Mutagenic Activity

Mammals, Microorganisms, Review, 79-4835

Carbamic Acid, Ethyl Ester

Lung Neoplasms

Co-carcinogenic Effect, 79-4982

Mutagenic Activity

Mammals, Microorganisms, Review, 79-4835

Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester

Adenocarcinoma

Asbestos, 79-4978

Asbestos

Co-carcinogenic Effect, 79-4978

Gastrointestinal Neoplasms

Fibrosarcoma, 79-4978

Leiomyosarcoma, 79-4978

Myosarcoma

Asbestos, 79-4978

Pancreatic Neoplasms

Carcinogenic Potential, 79-5373

Respiratory Tract Neoplasms

Adenoma, 79-4978

Uterine Neoplasms

Adenocarcinoma, 79-4978

Carbohydrates

Plasmacytoma

Immunoglobulins, Heavy Chain, 79-5265

Carbon

Virus, Moloney Murine Leukemia

Co-carcinogenic Effect, 79-4943

Carcinoembryonic Antigen

Breast Neoplasms

Ascites, Pleural Effusions, 79-5242

Digestive System Neoplasms

Ascites, Pleural Effusions, 79-5242

Neoplasm Metastasis, 79-5331

Serum Levels, 79-5331

Lung Neoplasms

Ascites, Pleural Effusions, 79-5242

Pneumonia

Ascites, Pleural Effusions, 79-5242

Carcinogen, Chemical

Adenosine Cyclic 3',5' Monophosphate

- Carcinogen, Chemical (cont'd)**
 Metabolism, Review, 79-4937
 Ames Test
 NADPH-Generating System, 79-4940
 S9 Fraction, Review, 79-4803
 Arsenic
 Occupational Hazard, Review, 79-4813
 Aryl Hydrocarbon Hydroxylases
 Enzyme Activation, Review, 79-4840
 Asbestos
 Occupational Hazard, Review, 79-4813
 Benzene
 Occupational Hazard, Review, 79-4813
 Bladder Neoplasms
 Glucuronidase, 79-4846
 13-*cis*-Retinoic Acid, 79-4846
 Cell Division
 Hepatocarcinogenesis, Review, 79-4938
 Cell Transformation, Neoplastic
 Dose-Response Study, Review, 79-4805
 Tissue Culture, Review, 79-4803
 Chemical Reactivity
 Quantum Mechanics, Review, 79-4915
 Chromium
 Occupational Hazard, Review, 79-4813
 Chromosome Aberrations
 Occupational Hazard, Review, 79-4917
 DNA Repair
 Cell Transformation, Neoplastic, Review, 79-4909
 Mutagenic Activity, Review, 79-4909
 Environmental Hazard
 Dose-Response Study, Review, 79-4805
 Ether, Chloromethyl Methyl
 Occupational Hazard, Review, 79-4813
 Ether, Dichloromethyl Methyl
 Occupational Hazard, Review, 79-4813
 Ethylene, Chloro-
 Occupational Hazard, Review, 79-4813
 Glutathione Transferases
 Metabolism, Review, 79-4841
 Guanosine Cyclic 3',5' Monophosphate
 Metabolism, Review, 79-4937
 Hepatoma
 Air Pollutants, 79-5019
 Ligands
 Hepatocarcinogenesis, Review, 79-4841
 Lymphoma
 Air Pollutants, 79-5019
 Neoplasms, Experimental
 Risk Evaluation, Review, 79-4806
 Nickel
 Occupational Hazard, Review, 79-4813
 Nitroso Compounds
 Isolation and Characterization, Review, 79-4927
 Occupational Hazard
 Identification, Review, 79-4920
 Prostatic Neoplasms
 Adenocarcinoma, 79-4853
 Tars
 Occupational Hazard, Review, 79-4813
 Thresholds
 Risk Factors, Review, 79-4807
- Carcinogen, Environmental**
 Bladder Neoplasms
 Glucuronidase, 79-4846
 Child
 Epidemiology, Review, 79-4815
- Carcinogen, Environmental (cont'd)**
 Chromosomes
 Cell Transplantation, Neoplastic, Review, 79-4866
 Cytochrome P-450
 Metabolism, Review, 79-4843
 Thresholds
 Risk Factors, Review, 79-4807
- Carcinoid Tumor**
 Intestinal Neoplasms
 Case Report, 79-5337
 Neoplasm Metastasis, 79-5337
 Neoplasms, Multiple Primary, 79-5337
- Carcinoma**
 Bladder Neoplasms
 Acetamide, *N*-Fluorenyl-, 79-4864
 1-Butanol, 4-(Butylnitrosamino)-, 79-4864
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-, 79-4864
 2-Naphthylamine, 79-4864
 Urea, Methyl Nitroso-, 79-4864
 Liver Neoplasms
 Benzene, 4-Allyl-1,2-(methylenedioxy)-, 79-5023
 Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
 Lung Neoplasms
 Chromium, 79-4946
 Colony Stimulating Factor, 79-5326
 Occupational Hazard, Review, 79-4854
 Pneumoconiosis, 79-5371
 Smoking, 79-5371
 Nose Neoplasms
 Nickel, 79-4948
 Prostatic Neoplasms
 Diagnosis, 79-5387
 Epidemiology, Sweden, 79-5387
 Salivary Gland Neoplasms
 Cellular Inclusions, 79-5013
 Nicotine, 1'-Demethyl-1'-nitroso-, 79-5013
 Stomach Neoplasms
 Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
 Case Report, Heterotropic Pancreas, 79-5335
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
 Thyroid Neoplasms
 Hereditary Diseases, 79-5299
 Hyperparathyroidism, 79-5300
 Uterine Neoplasms
 Diabetes Mellitus, 79-5383
 Epidemiology, 79-5383
 Isoantigens, 79-5243
 Obesity, 79-5383
 Virus, Shope Rabbit Papilloma
 DNA, Viral, 79-5150
 Neoplasm Metastasis, 79-5150
- Carcinoma, Acinar Cell**
see Carcinoma
- Carcinoma, Basal Cell**
 BCG Vaccination
 Case Report, 79-5105
 Cicatrix, 79-5105
 Cholanthrene, 3-Methyl-
 Lipids, 79-5052
 Dibenz(a,h)anthracene
 Lipids, 79-5052
 Necrosis
 Graft Rejection, 79-5271
 Precancerous Conditions

Carcinoma, Basal Cell (cont'd)
 Diagnosis and Treatment, Review, 79-4862
 Transplantation, Heterologous
 Histological Study, 79-5271
 Mouse, Nude, 79-5271

Carcinoma, Bronchiolar
 Suberosis
 Case Report, 79-5367

Carcinoma, Colloid
 Colonic Neoplasms
 Urinary Diversion, 79-5338

Carcinoma, Ehrlich Tumor
 Selenic Acid, Dipotassium Salt
 Growth, 79-4950
 Selenious Acid, Disodium Salt
 Growth, 79-4950
 Selenium Dioxide
 Growth, 79-4950

Carcinoma, Epidermoid
 Benz(a)anthracene, 7,12-Dimethyl-
 Lipids, 79-5052
 Benzo(a)pyrene
 Lipids, 79-5052
 Bladder Neoplasms
 Precancerous Conditions, 79-5341
 Burns
 Cicatrix, Review, 79-4860
 Cervix Neoplasms
 Cholanthrene, 3-Methyl-, 79-5075
 Ergocryptine, 2-Bromo-, 79-5075
 Estradiol, 79-5075
 Prolactin, 79-5075
 Cholanthrene, 3-Methyl-
 Lipids, 79-5052
 Digestive System Neoplasms
 Panfuran-S, 79-5011
 Esophageal Neoplasms
 Case Report, 79-5334
 Scleroderma, Systemic, 79-5333
 Head and Neck Neoplasms
 Case Report, 79-5311
 Neoplasm Metastasis, 79-5311
 Immunologic Deficiency Syndromes
 B-Lymphocytes, 79-5290
 Keratoacanthoma
 Precancerous Conditions, 79-5222
 Laryngeal Neoplasms
 Keratosis, 79-5325
 Leukoplakia, 79-5325
 Lung Neoplasms
 Chromium, 79-4946
 Epidemiology, 79-5370
 Smoking, 79-5368
 Tuberculosis, Pulmonary, 79-5328
 Nasopharyngeal Neoplasms
 Diagnosis, 79-5322
 Osteomyelitis
 Case Report, 79-5319
 Poikiloderma Congenitale
 Case Report, 79-5269
 Precancerous Conditions
 Diagnosis and Treatment, Review, 79-4862
 Skin Neoplasms
 Epidemiology, 79-5390
 Neoplasm Metastasis, 79-5390

Carcinoma, Epidermoid (cont'd)
 Psoriasis, 79-5104
 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
 Stomach Neoplasms
 Ethane, 1,2-Dichloro-, 79-4961
 Tracheal Neoplasms
 Case Report, 79-5107
 Tracheotomy, 79-5107
 Uterine Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-, 79-5051
 Virus, Herpes Simplex 1
 Seroepidemiology, Review, 79-4873
 Vulvar Neoplasms
 Condylomata Acuminata, 79-5233

Carcinoma In Situ
 Bladder Neoplasms
 Neoplasm Metastasis, Review, 79-4914
 Cervix Neoplasms
 Antibodies, Viral, 79-5175
 Virus, Herpes Simplex 2, 79-5193

Carcinoma, Mucinous
 Colonic Neoplasms
Schistosoma japonicum, 79-5339
 Urinary Diversion, 79-5114
 Intestinal Neoplasms
 Methane, Azoxy-, 79-4955

Carcinoma, Oat Cell
 Lung Neoplasms
 Epidemiology, 79-5370
 Smoking, 79-5368

Carcinoma, Papillary
 Bladder Neoplasms
 Animal Model, Rat, 79-4993
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 79-4993

Carcinoma, Transitional Cell
 Bladder Neoplasms
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 79-4993
 Precancerous Conditions, 79-5341
 Blood Groups
 Phenotype, 79-5283
 Histocompatibility Antigens
 Phenotype, 79-5283
 Kidney Neoplasms
p-Acetophenetidide, 79-5006
 Neoplasms, Multiple Primary
 Case Report, 79-5348
 Urogenital Neoplasms
 Neoplasms, Multiple Primary, 79-5348

Carrageen
 Intestinal Neoplasms
 Metaplasia, 79-5036

Carrier Proteins
 Acetamide, *N*-Fluorenyl-2-yl-
 Cell Membrane, 79-4985
 Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 Cell Membrane, 79-4985
 Estrone
 Cell Membrane, 79-4985
 Testosterone
 Cell Membrane, 79-4985

- Casein
 - Dysgammaglobulinemia
 - Antigen-Antibody Complex, 79-5240
- Cell Adhesion
 - Lymphocytes
 - Fibroblasts, 79-5251
 - L Cells, 79-5251
 - Virus, SV40
 - Actin, 79-5219
 - Cell Transformation, Neoplastic, 79-5219
 - Phospholipids, 79-5219
- Cell Aggregation
 - Fibrosarcoma
 - Monocytes, 79-5285
 - Neutrophils, 79-5285
 - Neoplasms, Experimental
 - Hemocytes, 79-5282
- Cell Differentiation
 - Bladder Neoplasms
 - Retinoic Acid, 79-5395
 - Cell Transformation, Neoplastic
 - Epithelium, Review, 79-4936
 - Mutation, Review, 79-4936
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-Epithelium, 79-5002
 - Nucleotidases
 - Lymphocytes, 79-5392
 - Plasmacytoma
 - Histocompatibility Antigens, 79-5264
 - Immunoglobulins, Surface, 79-5264
 - Viral Proteins, 79-5264
 - Virus, Harvey Murine Sarcoma
 - Bone Marrow, Adipocytes, 79-5144
 - Cortisol Acetate, 79-5144
 - Insulin, 79-5144
 - Virus, Herpes Lucke
 - IgG, 79-5126
 - Virus, Kirsten Murine Sarcoma
 - Bone Marrow, Adipocytes, 79-5144
 - Cortisol Acetate, 79-5144
 - Insulin, 79-5144
 - Virus, Moloney Murine Sarcoma
 - Bone Marrow, Adipocytes, 79-5144
 - Insulin, 79-5144
- Cell Division
 - Bladder Neoplasms
 - Glucuronidase, 79-4846
 - Carcinogen, Chemical
 - Hepatocarcinogenesis, Review, 79-4938
 - Hormones
 - Hepatocytes, Review, 79-4938
 - Lipoproteins
 - Hepatocytes, Review, 79-4938
 - Neurilemmoma
 - DNA, 79-5224
 - Nucleotides
 - Hepatocytes, Review, 79-4938
 - Synovioma
 - DNA, 79-5224
- Cell Fusion
 - Neuroblastoma
 - Virus, Vesicular Stomatitis, 79-5232
 - Virus, Mason-Pfizer Monkey
 - Cycloheximide, 79-5157
 - Cytosine, 1- β -D-Arabinofuranosyl-, 79-5157
- Cell Fusion (cont'd)
 - Ultraviolet Rays, 79-5157
 - Virus Replication, 79-5157
 - Virus, Vesicular Stomatitis
 - Glycoproteins, 79-5232
 - Temperature Sensitive Mutants, 79-5232
- Cell Membrane
 - Acetamide, *N*-Fluoren-2-yl-
 - Carrier Proteins, 79-4985
 - Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 - Carrier Proteins, 79-4985
 - Bladder Neoplasms
 - Neoplasm Metastasis, Review, 79-4914
 - Cell Transformation, Neoplastic
 - Glycoproteins, 79-5261
 - Estrone
 - Carrier Proteins, 79-4985
 - Hematopoietic Stem Cells
 - Glycoproteins, 79-5164
 - Lymphoma
 - Histocompatibility Antigens, 79-5270
 - Melanoma
 - Antigens, Neoplasm, 79-5276
 - Neuroblastoma
 - Isolation and Characterization, 79-5394
 - Phosphatidylinositols
 - Alkaline Phosphatase, 79-4835
 - Cell Cycle Kinetics, Review, 79-4835
 - Testosterone
 - Carrier Proteins, 79-4985
 - Virus, Epstein-Barr
 - Glycoproteins, 79-5164
 - Virus, Measles
 - Antibodies, Viral, 79-5228
 - Virus, Sendai
 - Glycoproteins, 79-5229
 - Phosphatidylcholines, 79-5229
 - Virus, SV40
 - Formaldehyde, 79-5220
 - Surface Charge, 79-5220
- Cell Membrane Permeability
 - Skin Neoplasms
 - Keratinocytes, 79-5398
 - Virus, Herpes Simplex 1
 - Chromium Release Assay, 79-5185
 - Immune Serums, 79-5185
 - Triton X 100, 79-5185
 - Virus, Polyoma
 - Virus, Sendai, 79-5206
- Cell Migration Inhibition
 - Bladder Neoplasms
 - Retinoic Acid, 79-5395
 - T-Lymphocytes
 - Colchicine, 79-5251
 - Cytochalasin B, 79-5251
 - Nitrous Acid, Sodium Salt, 79-5251
 - Macrophages
 - RNA, 79-5234
 - Virus, Herpes Simplex 1
 - Macrophages, 79-5181
- Cell Movement
 - Leukemia
 - T-Lymphocytes, 79-5251
 - T-Lymphocytes
 - Lymphocyte Culture Test, Mixed, 79-5251

Cell Survival

Glioma

- Embryonic Tissue, 79-4979
- Virus, Kirsten Murine Sarcoma
- Ethidium Bromide, 79-5128

Cell Transformation, Neoplastic

- Adenosine Cyclic 3',5' Monophosphate
- DNA Repair, 79-4937
- Alpha Fetoproteins
- Retrodifferentiation, Review, 79-4899
- 1,3-Butadiene, 2-Chloro-
- Cells, Cultured, 79-4967
- Carcinogen, Chemical
- Dose-Response Study, Review, 79-4805
- Tissue Culture, Review, 79-4803
- Cell Differentiation
- Epithelium, Review, 79-4936
- Mutation, Review, 79-4936
- Fetal Globulins
- Enzymes, Review, 79-4899
- Retrodifferentiation, Review, 79-4899
- Glycoproteins
- Cell Membrane, 79-5261
- Colony Formation, 79-5261
- Oncogenic Viruses
- Adenosine Cyclic 3',5' Monophosphate, 79-4937
- Adenyl Cyclase, 79-4937
- Urea, 1-(1-Naphthyl)-2-thio-
- Embryo, Hamster, 79-4984
- Virus, Avian Reticuloendotheliosis
- Bone Marrow, 79-5120
- Fibroblasts, 79-5120
- Virus, Cytomegalo
- Review, 79-4872
- Virus, Epstein-Barr
- Nonlymphoid Cells, Review, 79-4870
- Review, 79-4872
- Virus, Guinea Pig Herpes
- Nonlymphoid Cells, Review, 79-4870
- Virus, Herpes
- Nonlymphoid Cells, Review, 79-4870
- Review, 79-4872
- Virus, Herpes Simplex 1
- Thymidine Kinase, 79-5180
- Virus, Kirsten Murine Leukemia
- Millardia meltada*, 79-5140
- Virus, Kirsten Murine Sarcoma
- Virus, Helper, 79-5141
- Virus, Murine Sarcoma
- Millardia meltada*, 79-5140
- Virus, Murine Sarcoma-Leukemia
- Interferon, 79-5129
- Virus, Polyoma
- DNA, Viral, 79-5205
- Virus Replication, 79-5205
- Virus, Rauscher Murine Leukemia
- Glycoproteins, 79-5137
- Virus, Reticuloendotheliosis
- Chromosomes, 79-5119
- Virus, Rous Sarcoma
- Potassium, 79-5227
- Sodium, 79-5227
- Virus, SV40
- Cell Adhesion, 79-5219
- Glycoproteins, 79-5220
- Membrane Proteins, 79-5218

Cells, Cultured

- Acetamide, *N*-(Carbamoylmethyl)-2-diazo-
- DNA Repair, 79-4999
- Benzo(a)pyrene
- DNA, Binding, 79-5085
- Burkitt's Lymphoma
- Tumorigenicity, Review, 79-4891
- 1,3-Butadiene, 2-Chloro-
- Cell Transformation, Neoplastic, 79-4967
- Erythroleukemia
- Erythropoiesis, 79-5318
- Estradiol
- DNA, Binding, 79-5085
- Neuroblastoma
- Isolation and Characterization, 79-5394
- Radiation, Ionizing
- Aryl Hydrocarbon Hydroxylases, 79-5100
- Serine, Diazoacetate (Ester)
- DNA Repair, 79-4999

Cellular Inclusions

- Salivary Gland Neoplasms
- Carcinoma, 79-5013
- Sarcoma, Reticulum Cell
- IgG, 79-5297
- Immunoglobulins, Light Chain, 79-5297

Cervix Neoplasms

- Adenocarcinoma
- Estradiol, 79-5075
- Prolactin, 79-5075
- Carcinoma, Epidermoid
- Cholanthrene, 3-Methyl-, 79-5075
- Ergocryptine, 2-Bromo-, 79-5075
- Estradiol, 79-5075
- Prolactin, 79-5075
- Carcinoma In Situ
- Antibodies, Viral, 79-5175
- Virus, Herpes Simplex 2, 79-5193
- Ergocryptine, 2-Bromo-
- Neoplasm Invasiveness, 79-5075
- Virus, Cytomegalo
- Antibodies, Viral, 79-5175
- Virus, Herpes Simplex
- Antibodies, Viral, 79-5175
- Carcinogenic Potential, Review, 79-4882
- Virus, Herpes Simplex 2
- DNA-RNA Hybridization, 79-5193
- Precancerous Conditions, 79-5193
- RNA, Messenger, 79-5193
- Seroepidemiology, Review, 79-4873

CFT 1201

- see 4-Pentoic Acid, 2-(Diethylamino)ethyl-2-phenyl-2-(2-propene)-

Chemotaxis

- Aflatoxin B1
- Leukocytes, 79-5033

Chloramphenicol

- Chromosome Abnormalities
- Cell Cycle Kinetics, 79-5043
- Lymphocytes
- Chromosome Abnormalities, 79-5043
- Proteins
- Chromosome Abnormalities, 79-5043
- Teratoid Tumor
- Genetics, 79-5391

5 β -Cholan-24-oic Acid, 3 α ,7 α -Dihydroxy-

- Colonic Neoplasms
- Hydrazine, 1,2-Dimethyl-, 79-4977
- Hydrazine, 1,2-Dimethyl-
- Co-carcinogenic Effect, 79-4977

Cholangioma

- Liver Neoplasms
- Thorium Dioxide, 79-5110

Cholanthrene, 3-Methyl-

- Adrenal Cortex
- Aryl Hydrocarbon Hydroxylases, 79-5073
- Aryl Hydrocarbon Hydroxylases
- Genetics, Mouse, Reveiw, 79-4840
- Lung, Mouse, 79-5025
- Tissue Distribution, Rat, 79-5074
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
- Nucleoside Adducts, 79-5063
- Benzo(a)pyrene-6-methanol
- DNA, Binding, 79-5065
- Microsomes, Liver, 79-5065
- Carcinoma, Basal Cell
- Lipids, 79-5052
- Carcinoma, Epidermoid
- Lipids, 79-5052
- Cervix Neoplasms
- Carcinoma, Epidermoid, 79-5075
- Cytochrome P-450
- Metabolism, Review, 79-4840
- Diethylamine, N-Nitroso-
- Nucleic Acids, 79-4990
- Fibrosarcoma
- Rat, Germfree, Review, 79-4918
- Immunization
- Antigen-Antibody Reactions, 79-5054
- Neoplasms, Experimental
- Antigen-Antibody Reactions, 79-5054
- Immunization, 79-5054
- Transplantation Immunology, 79-5235
- Virus, Herpes Simplex 2, 79-5196
- Sarcoma
- Axilla, Groin, Mouse, 79-5053
- Histocompatibility Antigens, 79-5248
- Immunosuppression, 79-5053
- Skin Neoplasms
- Lipids, 79-5052
- Virus, Herpes Simplex 2
- Co-carcinogenic Effect, 79-5196

Cholecystitis

- Bile Duct Neoplasms
- Myoblastoma, 79-5329

Cholelithiasis

- Estrogenic Substances, Conjugated
- Drug Therapy, 79-5354

Cholera Toxin

- Butyric Acid, Sodium Salt
- Binding Sites, 79-4966
- Erythroleukemia
- Binding Sites, 79-4966
- Fatty Acids
- Binding Sites, 79-4966
- HeLa Cells
- Binding Sites, 79-4966

Cholesterol

- Aryl Hydrocarbon Hydroxylases
- Tissue Distribution, Rat, 79-5074
- Colonic Neoplasms
- Epidemiology, Review, 79-4928
- Estrone
- Membranes, Binding, 79-4985
- Melanoma
- Metabolism, 79-5399
- Testosterone
- Membranes, Binding, 79-4985

Chondroma

- Bone Neoplasms
- Ethylene, Chloro-, 79-4808

Choriocarcinoma

- Gonadotropins, Chorionic
- Endocrine Abnormalities, Review, 79-4850
- Hydatidiform Mole
- Karyotyping, 79-5350
- Neoplasm Metastasis, 79-5350
- Testicular Neoplasms
- Gonadotropins, 79-4855
- Uterine Neoplasms
- Hydatidiform Mole, 79-5350

Chromatids

- Butyric Acid, 4-(p-Bis(2-chloroethyl)aminophenyl)-
- Chromosome Aberrations, 79-4994
- Cyclophosphamide
- Chromosome Aberrations, 79-4994
- Fish, 79-4998
- Malathion
- Chromosome Aberrations, 79-4971
- Fibroblasts, 79-4971
- Methanesulfonic Acid, Methyl Ester
- Fish, 79-4998
- Mutagens
- Fetus, Mouse, 79-4941
- Neutral Red
- Fish, 79-4998
- Prednisolone
- Chromosome Aberrations, 79-4994
- Purine-6-thiol
- Chromosome Aberrations, 79-4994
- Radiation, Ionizing
- Lymphocytes, 79-5101
- Uridine, 5-Bromo-2'-deoxy-
- Fish, 79-4998
- Vinblastine Sulfate
- Chromosome Aberrations, 79-4994

Chromatin

- Virus, Herpes Simplex 1
- Poly ADP Ribose Polymerase, 79-5176

Chromium

- Bronchitis
- Occupational Hazard, 79-4946
- Carcinogen, Chemical
- Occupational Hazard, Review, 79-4813
- Lung Neoplasms
- Adenocarcinoma, 79-4946
- Carcinoma, 79-4946
- Carcinoma, Epidermoid, 79-4946
- Occupational Hazard, 79-4946, 79-5369
- Precancerous Conditions, 79-4946
- Pulmonary Emphysema
- Occupational Hazard, 79-4946

Chromium (cont'd)

- Pulmonary Fibrosis
Occupational Hazard, 79-4946
- Tobacco
Heavy Metal Levels, 79-4944

Chromosome Aberrations

- Acetic Acid, (2,4,5-Trichlorophenoxy)-
Teratogenic Effects, Review, 79-4832
- Anemia, Aplastic
Chromosomes, Human, 1-3, 79-5288
Thrombocytosis, 79-5288
- 1,3-Benzenedicarbonitrile, 2,4,5,6-Tetrachloro-
Hordeum vulgare, 79-4972
- Butyric Acid, 4-(p-Bis(2-chloroethyl)aminophenyl)-
Chromatids, 79-4994
- Carcinogen, Chemical
Occupational Hazard, Review, 79-4917
- Crotonic Acid, 3-Hydroxy-, Methyl Ester, Dimethyl
Phosphate
Hordeum vulgare, 79-4972
- Cyclophosphamide
Bone Marrow, 79-5079
Chromatids, 79-4994
- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-
Bone Marrow, 79-4960
Nitrogen Monoxide, 79-4960
Spermatozoa, 79-4960
- Ethanol, 2-Chloro-
Mutagenic Activity, 79-4957
- Ethylene, Chloro-
Mutagenic Activity, Review, 79-4808
- Ethylene Glycol
Mutagenic Activity, 79-4957
- Ethylene Oxide
Mutagenic Activity, 79-4957
Mutagenic Activity, Review, 79-4809
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
Erythrocytes, 79-4996
Lymphocytes, 79-4996
Micronucleus Test, 79-4996
- Kidney Diseases
Cyclophosphamide, 79-4994
Purine-6-thiol, 79-4994
- Light
Photobiology, Review, 79-4856
- Lung Neoplasms
Sex Chromosome, 79-5327
- Malathion
Chromatids, 79-4971
- Methanesulfonic Acid, Methyl Ester
Micronucleus Test, 79-4996
- Mutagens
Erythrocytes, 79-4908
Genetics, Review, 79-4835
Micronucleus Test, 79-4908
Screening Tests, Review, 79-4801
- Nitrogen Monoxide
Bone Marrow, 79-4960
Spermatozoa, 79-4960
- Phosphoric Acid, Trimethyl Ester
Mutagenic Activity, Review, 79-4816
- Prednisolone
Chromatids, 79-4994
- Propane, 1,2-Epoxy-
Lymphocytes, 79-4964
- Purine-6-thiol
Chromatids, 79-4994

Chromosome Aberrations (cont'd)

- Radiation, Ionizing
Cell Cycle Kinetics, 79-5101
Plant Agglutinins, 79-5101
Uridine, 5-Bromo-2'-deoxy-, 79-5101
- Radioactive Fallout
B-Lymphocytes, 79-5096, 79-5097
T-Lymphocytes, 79-5096
Virus, Epstein-Barr, 79-5096, 79-5097
- 4,4'-Stilbenediol, α,α' -Diethyl-, Bis(dihydrogen phosphate)
Bone Marrow, 79-5079
- Urea, 3-(p-Chlorophenyl)-1,1-dimethyl-
Hordeum vulgare, 79-4972
- Vinblastine Sulfate
Chromatids, 79-4994

Chromosome Abnormalities

- Chloramphenicol
Cell Cycle Kinetics, 79-5043
Lymphocytes, 79-5043
Proteins, 79-5043
- Erythroleukemia
Azathioprine, 79-5042

Chromosomes

- Carcinogen, Environmental
Cell Transplantation, Neoplastic, Review, 79-4866
- Fibrosarcoma
Hybrid Cells, 79-5286
- Leukemia
Genes, Recessive, Review, 79-4916
- Neoplasms
Genes, Recessive, Review, 79-4916
- Oncogenic Viruses
Cell Transplantation, Neoplastic, Review, 79-4866
Enzyme Induction, Review, 79-4866
Hybrid Cells, Review, 79-4916
- 12-O-Tetradecanoylphorbol-13-acetate
Mitosis, Review, 79-4838
- Virus, Rauscher Murine Leukemia
Viral Proteins, 79-5135
- Virus, Reticuloendotheliosis
Cell Transformation, Neoplastic, 79-5119
DNA, Viral, 79-5119

Chromosomes, Human, 1-3

- Anemia, Aplastic
Chromosome Aberrations, 79-5288
- Aryl Hydrocarbon Hydroxylases
Hybrid Cells, Review, 79-4839

Chromosomes, Human, 21-22

- Leukemia, Myelocytic
Diagnosis, 79-5292
Polycythemia Vera, 79-5292

Cicatrix

- Carcinoma, Basal Cell
BCG Vaccination, 79-5105
- Neoplasm Metastasis
Capillaries, 79-5287

Cimetidine

- Stomach Neoplasms
Case Report, 79-5040
Dose-Response Study, Rat, 79-5039

Clostridiopeptidase A

- Basement Membrane
Neoplasm Metastasis, 79-5317

- Clostridiopeptidase A (cont'd)**
 - Collagen
 - Basement Membrane, 79-5317
 - Sarcoma
 - Enzymatic Activity, 79-5317
- Clostridium botulinum***
 - Nitrous Acid, Sodium Salt
 - Spore Germination, 79-4975
 - Sorbic Acid
 - Spore Germination, 79-4975
- Coal**
 - Lung Neoplasms
 - Occupational Hazard, 79-5371
- Coal Tar**
 - Ames Test
 - Mutagenic Activity, 79-5067
 - Therapeutic Preparations, 79-5067
- Cobalamine, Methyl-**
 - Platinum, Tetrachloro-
 - Reaction Products, 79-4949
- Cobalt**
 - Rhabdomyosarcoma
 - Cortisol, 79-5070
- Coformycin**
 - Neuroblastoma
 - Metabolism, 79-5393
- Colchicine**
 - T-Lymphocytes
 - Cell Migration Inhibition, 79-5251
 - Neuroblastoma
 - Isolation and Characterization, 79-5394
- Collagen**
 - Clostridiopeptidase A
 - Basement Membrane, 79-5317
- Colloidal Gold**
 - see Gold
- Colonic Neoplasms**
 - Adenocarcinoma
 - Hydrazine, 1,2-Dimethyl-, 79-4977
 - Methane, Azoxy-, 79-4955
 - Urinary Diversion, 79-5112, 79-5113, 79-5338
 - Adenoma
 - Hydrazine, 1,2-Dimethyl-, 79-4977
 - Carcinoma, Colloid
 - Urinary Diversion, 79-5338
 - Carcinoma, Mucinous
 - Schistosoma japonicum*, 79-5339
 - Urinary Diversion, 79-5114
 - Cholesterol
 - Epidemiology, Review, 79-4928
 - Cytotoxins
 - Antigen-Antibody Complex, 79-5239
 - Diet
 - Epidemiology, Review, 79-4926
 - Dietary Fats
 - Epidemiology, Review, 79-4927, 79-4928
 - Hydrazine, 1,2-Dimethyl-
 - 5 β -Cholan-24-oic Acid, 3 α ,7 α -Dihydroxy-, 79-4977
 - IgG
 - Antigen-Antibody Complex, 79-5239
 - Methane, Azoxy-
 - Pancreaticobiliary Diversion, 79-4955
- Colonic Neoplasms (cont'd)**
 - Ureterosigmoidostomy
 - Case Report, 79-5338
 - Urinary Diversion
 - Case Report, 79-5112, 79-5113, 79-5114
- Complement**
 - Immune Serums
 - Strain Difference, Rabbit, 79-5237
 - Leukemia, Lymphocytic
 - Lymphocytotoxicity, 79-5237
 - Lymphosarcoma
 - Immune Serums, 79-5237
 - Lymphocytotoxicity, 79-5237
 - Sarcoma
 - Lymphocytotoxicity, 79-5237
 - Virus, Herpes Simplex 1
 - Hemolysins, 79-5185
- Complement 3**
 - Virus, Epstein-Barr
 - Lymphocyte Transformation, Review, 79-4890
 - B-Lymphocytes, 79-5171
- Concanavalin A**
 - Breast Neoplasms
 - Lymphocyte Transformation, 79-5254
 - Burkitt's Lymphoma
 - Binding Sites, Review, 79-4905
 - Gastrointestinal Neoplasms
 - Lymphocyte Transformation, 79-5254
 - Hodgkin's Disease
 - Binding Sites, Review, 79-4905
 - Lymphocytes, 79-4905
 - Immune Response
 - Rat, Nude, 79-5259
 - Leukemia, Lymphocytic
 - Binding Sites, Review, 79-4905
 - Lymphoma
 - Binding Sites, Review, 79-4905
 - Neuroblastoma
 - Isolation and Characterization, 79-5394
 - Lymphocyte Transformation, 79-5255
- Condylomata Acuminata**
 - Vulvar Neoplasms
 - Carcinoma, Epidermoid, 79-5233
 - Case Report, 79-5233
- Contraceptives, Oral**
 - Breast Neoplasms
 - Epidemiology, Review, 79-4931
 - Gynecologic Neoplasms
 - Epidemiology, Review, 79-4931
 - Hepatoma
 - Co-carcinogenic Effect, Review, 79-4929
 - Liver Neoplasms
 - Adenoma, 79-4931, 79-5089
 - Case Report, 79-5086
 - Epidemiology, Review, 79-4931
- Copper**
 - Ascorbic Acid
 - Metabolism, Review, 79-4844
 - Brain Diseases, Metabolic
 - Proteins, Kidney, 79-4945
 - Tissue Distribution, Mouse, 79-4945
 - Quinoline, 4-(Hydroxyamino)-, 1-Oxide
 - DNA, Binding, 79-5008
 - Tobacco

Copper (cont'd)

- Heavy Metal Levels, 79-4944
- Vitamin E
- Metabolism, Review, 79-4844

Coronene

- Ames Test
- Food Contamination, 79-5066

Corticotropin

- Aryl Hydrocarbon Hydroxylases
- Adrenal Cortex, Rat, 79-5073
- Pancreatic Neoplasms
- Gastrin, 79-5076
- Zollinger-Ellison Syndrome, 79-5076

Cortisol

- Metabolism, Inborn Errors
- Histocompatibility Antigens, 79-5306
- Rhabdomyosarcoma
- Cobalt, 79-5070
- Proteins, Metabolism, 79-5070
- RNA, Transfer, Methyltransferases, 79-5070

Cortisol Acetate

- Virus, Harvey Murine Sarcoma
- Cell Differentiation, 79-5144
- Virus, Kirsten Murine Sarcoma
- Cell Differentiation, 79-5144
- Virus, Moloney Murine Sarcoma
- Bone Marrow, Adipocytes, 79-5144

Cortisone Acetate

- T-Lymphocytes
- Radiation, Ionizing, 79-4903
- Virus, Cytomegalo
- Virus Activation, 79-5158
- Virus Replication, 79-5158

Corynebacterium parvum

- Virus, Marek's Disease Herpes
- Hypersensitivity, Delayed, 79-5125

***p*-Cresol, 2,6-Di-*tert*-butyl-**

- Benzo(a)pyrene
- Aryl Hydrocarbon Hydroxylases, 79-5074

Crotonic Acid, 3-Hydroxy-, Methyl Ester, Dimethyl Phosphate

- Chromosome Aberrations
- Hordeum vulgare*, 79-4972

Cushing's Syndrome

- Disgerminoma
- Endocrine Abnormalities, Review, 79-4855

Cycloheptylamine

- Microsomes, Liver
- Deamination Products, 79-4970

Cyclohexanesulfonic Acid, Monosodium Salt

- Bladder Neoplasms
- Co-carcinogenic Effect, Review, 79-4864

4-Cyclohexene-1,2-dicarboximide, *N*-(Trichloromethyl)thio-

- Mutagenic Activity
- Mammals, Microorganisms, Review, 79-4835

Cyclohexene Oxide

- Benzene
- Phosphodiesterases, 79-4968
- Phosphates
- Diol Epoxides, 79-4968

Cycloheximide

- Adenosine Triphosphatase
- Microsomes, Liver, 79-4969
- Glucosylphosphatase
- Microsomes, Liver, 79-4969
- Hepatoma
- DNA Replication, 79-5057
- Melanoma
- Melanin, 79-5231
- Microsomes, Liver
- DNA Replication, 79-5057
- Mixed Function Oxidases
- Microsomes, Liver, 79-4969
- Virus, Epstein-Barr
- B-Lymphocytes, 79-5161
- Virus, Mason-Pfizer Monkey
- Cell Fusion, 79-5157

Cyclohexylamine

- Microsomes, Liver
- Deamination Products, 79-4970
- NADP
- Metabolism, 79-4970
- Oxygen
- Metabolism, 79-4970

Cyclopentylamine

- Microsomes, Liver
- Deamination Products, 79-4970

Cyclophosphamide

- Bladder Neoplasms
- Epidemiology, Review, 79-4817
- Chromatids
- Chromosome Aberrations, 79-4994
- Fish, 79-4998
- Chromosome Aberrations
- Bone Marrow, 79-5079
- Kidney Diseases
- Chromosome Aberrations, 79-4994
- Leukemia
- Epidemiology, Review, 79-4817
- Leukemia, Myeloblastic
- Radiation, Ionizing, 79-4995
- Lymphoma
- Epidemiology, Review, 79-4817

Cyclosporin A

- T-Lymphocytes
- Lymphocyte Transformation, Review, 79-4904
- Transplantation, Homologous
- Immune Response, Review, 79-4904

Cylindroma

- Neoplasms, Multiple Primary
- Ultrastructural Study, 79-5321

Cyroglobulins

- Sarcoma, Reticulum Cell
- IgA, 79-5272
- IgG, 79-5272

Cystadenocarcinoma

- Ovarian Neoplasms
- Genetics, 79-5347

Cystadenoma

- Ovarian Neoplasms
- Epidemiology, 79-5382
- Pancreatic Neoplasms
- Hippel-Lindau Disease, 79-5303

- Cysts**
 - Ovarian Neoplasms
 - Epidemiology, 79-5382
- Cytochalasin B**
 - Glucose, 2-Deoxy-
 - Metabolism, 79-5077
 - T-Lymphocytes
 - Cell Migration Inhibition, 79-5251
- Cytochrome P-450**
 - Benzo(a)pyrene
 - Metabolism, Review, 79-4840
 - Carcinogen, Environmental
 - Metabolism, Review, 79-4843
 - Cholanthrene, 3-Methyl-
 - Metabolism, Review, 79-4840
 - Ethyl Alcohol
 - Microsomes, Liver, 79-4956
 - Lead
 - Carcinogenic Potential, Review, 79-4814
 - Polycyclic Hydrocarbons
 - Metabolism, Review, 79-4840
- Cytosine, 2,2'-Anhydro-1- β -D-arabinofuranosyl-**
 - Virus, Kirsten Murine Sarcoma
 - Virus Replication, 79-5143
- Cytosine, 1- β -D-Arabinofuranosyl-**
 - Virus, Epstein-Barr
 - B-Lymphocytes, 79-5161
 - Virus, Kirsten Murine Sarcoma
 - Virus Replication, 79-5143
 - Virus, Mason-Pfizer Monkey
 - Cell Fusion, 79-5157
- Cytotoxins**
 - Colonic Neoplasms
 - Antigen-Antibody Complex, 79-5239
 - Melanoma
 - Antigen-Antibody Complex, 79-5239
- Deoxyribonuclease**
 - Virus, Herpes Simplex 1
 - Antibody Specificity, 79-5191
 - Virus, Herpes Simplex 2
 - Antibody Specificity, 79-5191
- Desmoid Tumor**
 - see Fibroma
- Detergents**
 - Environmental Pollutants
 - Quantitation Method, Review, 79-4837
- Deuterium**
 - Toluene-2,4-diamine
 - Mutagenic Activity, 79-5022
- Dexamethasone**
 - Glucose, 2-Deoxy-
 - Metabolism, 79-5077
- Diabetes Mellitus**
 - Pancreatic Neoplasms
 - Epidemiology, France, 79-5373
 - Uterine Neoplasms
 - Carcinoma, 79-5383
 - Epidemiology, Review, 79-4933
- N-Diazoacetyl Derivatives**
 - Amino Acids
 - DNA Repair, 79-4999
- N-Diazoacetyl Derivatives (cont'd)**
 - Norleucine, 6-Diazo-5-oxo-
 - DNA Repair, 79-4999
- N-Diazoacetyl-glycine Amide**
 - see Acetamide, N-(Carbamoylmethyl)-2-diazo-
- Dibenz(a,h)acridine**
 - Adenoma
 - Iron Oxide, 79-4947
 - Iron Oxide
 - Co-carcinogenic Effect, Hamster, 79-4947
 - Lymphoma
 - Iron Oxide, 79-4947
 - Papilloma
 - Iron Oxide, 79-4947
 - Respiratory Tract Neoplasms
 - Iron Oxide, 79-4947
- Dibenz(a,h)anthracene**
 - Carcinoma, Basal Cell
 - Lipids, 79-5052
 - Skin Neoplasms
 - Lipids, 79-5052
- Dibenzo-p-dioxin, 1,2,3,6,7,8-Hexachloro-**
 - Ultraviolet Rays
 - Tetra and Penta Isomers, 79-5094
- Dibenzo-p-dioxin, 1,2,3,7,8,9-Hexachloro-**
 - Ultraviolet Rays
 - Tetra and Penta Isomers, 79-5094
- Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-**
 - Acetic Acid, (2,4,5-Trichlorophenoxy)-
 - Teratogenic Effects, Review, 79-4832
 - Adrenal Cortex
 - Aryl Hydrocarbon Hydroxylases, 79-5073
 - Aryl Hydrocarbon Hydroxylases
 - Liver, Intestines, 79-5095
 - Calcium
 - Metabolism, Rat, 79-5095
 - Environmental Hazard
 - Epidemiology, Review, 79-4811
 - Iron
 - Metabolism, Rat, 79-5095
- Dieldrin**
 - Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
 - Epoxide Hydratases, 79-5068
 - Oxygenases, 79-5068
 - Metabolism
 - Analogues, 79-5068
 - Microsomes, Liver
 - Metabolism, 79-5068
- Diet**
 - p-Acetophenetidine
 - Nitrosation, Review, 79-4818
 - Brain Neoplasms
 - Restriction, 79-5397
 - Breast Neoplasms
 - Epidemiology, Review, 79-4930
 - Colonic Neoplasms
 - Epidemiology, Review, 79-4926
 - Digestive System Neoplasms
 - Epidemiology, Review, 79-4930
 - Peptide Hydrolases, 79-4930
 - Hepatoma
 - Restriction, 79-5397
 - Mammary Neoplasms, Experimental

Diet (cont'd)

- Adenoma, 79-5397
- Pituitary Neoplasms
 - Adenoma, 79-5397
- Skin Neoplasms
 - Restriction, 79-5397
- Stomach Neoplasms
 - Epidemiology, Review, 79-4926
- Testicular Neoplasms
 - Restriction, 79-5397
- Thymus Neoplasms
 - Restriction, 79-5397

Dietary Fats

- Breast Neoplasms
 - Epidemiology, Review, 79-4927, 79-4928
- Colonic Neoplasms
 - Epidemiology, Review, 79-4927, 79-4928
- Intestinal Neoplasms
 - Epidemiology, Review, 79-4913
- Prostatic Neoplasms
 - Epidemiology, Review, 79-4927

Dietary Proteins

- Lung Neoplasms
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024

Diethylamine, *N*-Nitroso-

- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Nucleic Acids, 79-4990
- Cholanthrene, 3-Methyl-
 - Nucleic Acids, 79-4990
- Food Contamination
 - Carcinogenic Potential, Review, 79-4828
- Laryngeal Neoplasms
 - Dose-Response Study, Hamster, 79-4991
 - Polyps, 79-4991
- Nucleic Acids
 - Alkylation, 79-4990
 - Liver, Mouse, 79-4990
- 4-Pentoic Acid, 2-(Diethylamino)ethyl-2-phenyl-2-(2-propene)-
 - Nucleic Acids, 79-4990
- Tracheal Neoplasms
 - Dose-Response Study, Hamster, 79-4991
 - Polyps, 79-4991
- Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester, HCl
 - Nucleic Acids, 79-4990

Digestive System Neoplasms

- Adenocarcinoma
 - Neoplasms, Multiple Primary, 79-5348
 - Panfuran-S, 79-5011
- Carcinoembryonic Antigen
 - Ascites, Pleural Effusions, 79-5242
 - Neoplasm Metastasis, 79-5331
 - Serum Levels, 79-5331
- Carcinoma, Epidermoid
 - Panfuran-S, 79-5011
- Diet
 - Epidemiology, Review, 79-4930
 - Peptide Hydrolases, 79-4930
- Ethylene, Chloro-
 - Carcinogenic Activity, Review, 79-4808
- Neoplasms, Multiple Primary
 - Epidemiology, 79-5355
- Occupational Hazard
 - Epidemiology, 79-5361

Digestive System Neoplasms (cont'd)

- Papilloma
 - Panfuran-S, 79-5011

Digitalis

- Breast Neoplasms
 - Receptors, Estrogen, Review, 79-4848
- Gynecomastia
 - Structure-Activity Relationship, Review, 79-4848

Digoxin

- Breast Neoplasms
 - Receptors, Estrogen, Review, 79-4848

Dihydrosafrole

- see Benzene, 1,2-(Methylenedioxy)-4-propyl-

Dimethylamine, *N*-Nitroso-

- Ames Test
 - Arabinose Resistance, 79-4988
- Ammonium Sulfate
 - Metabolism, 79-4989
 - Mixed Function Oxidases, 79-4989
- Food Contamination
 - Carcinogenic Potential, Review, 79-4828
- Microsomes, Liver
 - Metabolism, 79-4989
- Salmonella typhimurium*
 - Host-Mediated Assay, 79-4988
 - Mutation, 79-4988

p-Dioxane

- Iron
 - Metabolism, Rat, 79-5095

Dipropylamine, 2,2'-Dihydroxy-*N*-nitroso-

- Pancreatic Neoplasms
 - Carcinogenic Potential, 79-5373

Disgerminoma

- Cushing's Syndrome
 - Endocrine Abnormalities, Review, 79-4855
- Hypercalcemia
 - Endocrine Abnormalities, Review, 79-4855
- Ovarian Neoplasms
 - Age Factors, 79-5382
 - Turner's Syndrome, 79-5345
- Testicular Neoplasms
 - Epidemiology, Jamaica, 79-5388
 - Gonadotropins, 79-4855

DNA

- Benz(a)anthracene, 7,12-Dimethyl-
 - Cell Cycle Kinetics, 79-5044
- Benzo(a)pyrene
 - Carcinogenic Metabolite, Review, 79-4838
- Ethylene, Chloro-
 - Carcinogenic Metabolite, Review, 79-4920
- Ethylene, Trichloro-
 - Carcinogenic Metabolite, Review, 79-4920
- Leukemia, Myeloblastic
 - Transformation, Genetic, 79-5224
- Neurilemmoma
 - Cell Division, 79-5224
- Rhabdomyosarcoma
 - Synovioma, 79-5224
- Synovioma
 - Cell Division, 79-5224
- Virus, C-Type RNA Tumor
 - Nucleoproteins, 79-5225
 - Uridine, 5-Bromo-2'-deoxy-, 79-5225

- DNA, Bacterial**
 Zearalenone
Bacillus subtilis, 79-5029
- DNA, Circular**
 Virus, Epstein-Barr
 Nucleic Acid Renaturation, 79-5160
- DNA Polymerase**
 Virus, Rauscher Murine Leukemia
 Enhancing Factor, Egg Fluids, 79-5136
- DNA Repair**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Chromatids, Review, 79-4829
 Acetamide, *N*-(Carbamoylmethyl)-2-diazo-
 Cells, Cultured, 79-4999
 Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
Escherichia coli, 79-5000
 Adenosine Cyclic 3',5' Monophosphate
 Cell Transformation, Neoplastic, Review, 79-4937
 Amino Acids
N-Diazaoacetyl Derivatives, 79-4999
 Astrocytoma
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5200
 Ataxia Telangiectasia
 Bleomycin, 79-5091
 Brain Neoplasms
 Ultraviolet Rays, 79-5200
 Virus, Adeno 5, 79-5200
 Carcinogen, Chemical
 Cell Transformation, Neoplastic, Review, 79-4909
 Mutagenic Activity, Review, 79-4909
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
Escherichia coli, 79-5000
 Glioblastoma Multiforme
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5200
 Methanesulfonic Acid, Ethyl Ester
Saccharomyces cerevisiae, 79-4953
 Methanesulfonic Acid, Methyl Ester
Saccharomyces cerevisiae, 79-4953
 Mutagens
 Screening Tests, Review, 79-4801
 Mutation
Saccharomyces cerevisiae, 79-4953
 Neoplasms
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5200
 Norleucine, 6-Diazo-5-oxo-
N-Diazaoacetyl Derivatives, 79-4999
 Quinoline, 4-Nitro-, 1-Oxide
 Chromatids, Review, 79-4829
 Serine, Diazoacetate (Ester)
 Cells, Cultured, 79-4999
 Thiazole, 2-Amino-4-(5-nitro-2-furyl)-
Escherichia coli, 79-5000
 Ultraviolet Rays
 Chromatids, Review, 79-4829
 Virus, Adeno 5
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5200
 Virus, Herpes
 Co-carcinogenic Effect, Review, 79-4880
- DNA Replication**
 Bladder Neoplasms
 Retinoic Acid, 79-5395
 Cantharidin
 Cell Cycle Kinetics, 79-4973
 Epidermis, Mouse, 79-4973
 Hepatoma
- DNA Replication (cont'd)**
 Barbituric Acid, 5-Ethyl-5-phenyl-, 79-5057
 Benzo(a)pyrene, 79-5057
 Cycloheximide, 79-5057
 Urea, Methyl Nitroso-, 79-5057
 Leukemia, Lymphocytic
 Lymphocytes, 79-5250
 T-Lymphocytes, 79-5250
 Light
 Photobiology, Review, 79-4856
 Mammary Neoplasms, Experimental
 LS 1727, 79-5046
 Prolactin, 79-5047
 Ultraviolet Rays
 Photobiology, Review, 79-4856
 Virus, Adeno 2
 DNA, Viral, 79-5198
 Temperature Sensitive Mutants, 79-5198
 Virus, Epstein-Barr
 B-Lymphocytes, 79-5161
 Virus, Herpes
 Virus, Recombinant, Review, 79-4867
 Virus, Herpes Simplex 1
 Mitogens, 79-5187
 Poly ADP Ribose Polymerase, 79-5176
 Virus, Herpes Simplex 2
 Mitogens, 79-5187
 Virus, Moloney Murine Leukemia
 Magnesium, 79-5132
 Manganese, 79-5132
 Nucleotides, 79-5132
 Virus, Polyoma
 Cell Nucleus, 79-5203
 Endonucleases, 79-5203
 RNA, Messenger, 79-5204
 Virus, Rauscher Murine Leukemia
 Carcinogenic Activity, 79-5136
 Virus, SV40
 Antigens, Neoplasm, 79-5216
 Temperature Sensitive Mutants, 79-5216
 12-*O*-Tetradecanoylphorbol-13-acetate, 79-5216
- DNA, Single Stranded**
 Virus, Kilham Rat
 Nucleotide Sequence, 79-5146
- DNA, Viral**
 Carcinoma
 Virus, Shope Rabbit Papilloma, 79-5150
 Fibroma
 Virus, Bovine Papilloma, 79-5156
 Herpes Zoster
 Isolation and Characterization, Review, 79-4887
 Papilloma
 Virus, Shope Rabbit Papilloma, 79-5150
 Soft Tissue Neoplasms
 Virus, Bovine Papilloma, 79-5156
 Virus, Adeno 2
 DNA Replication, 79-5198
 Virus, Bovine Papilloma
 Nucleic Acid Hybridization, 79-5156
 Virus, Epstein-Barr
 Cell Transformation, Neoplastic, Review, 79-4871
 79-4889
 Centrifugation, Review, 79-4893
 Endonucleases, 79-5160
 Epithelial Cells, 79-5169
 Epithelial Cells, Lymphocytes, Review, 79-4896

DNA, Viral (cont'd)

- Integration, Review, 79-4893
- Plasmids, Review, 79-4867
- Strain Difference, Review, 79-4889
- Virus, Herpes
 - Isolation and Characterization, Review, 79-4875
 - Nucleic Acid Homology, Review, 79-4879
- Virus, Herpes Simplex
 - Cell Transformation, Neoplastic, Review, 79-4871
 - Thymidine Kinase, 79-4871
 - Virus, Recombinant, Review, 79-4868
- Virus, Herpes Simplex 1
 - Nucleotide Sequence, 79-5188, 79-5189
 - Peptides, 79-5189
 - RNA, Messenger, 79-5177
 - Virus, Recombinant, 79-5189
- Virus, Herpes Simplex 2
 - Nucleotide Sequence, 79-5189
 - Peptides, 79-5189
 - Virus, Recombinant, 79-5189
- Virus, Moloney Murine Leukemia
 - Endonucleases, 79-5133
 - Fibroblasts, Integration Sites, 79-5133
- Virus, Polyoma
 - Bacteriophages, 79-5208
 - Cell Transformation, Neoplastic, 79-5205
 - Extrachromosomal Inheritance, 79-5208
 - Lysosomes, 79-5206
- Virus, Reticuloendotheliosis
 - Chromosomes, 79-5119
- Virus, Rous Sarcoma
 - Nucleic Acid Synthesis, 79-5115
 - Transformation, Genetic, 79-5115
- Virus, Shope Rabbit Papilloma
 - Neoplasm Metastasis, 79-5150
- Virus, SV40
 - Deletion Mutants, 79-5212, 79-5213, 79-5215
 - Nucleotide Sequence, 79-5212
 - Virus Replication, 79-5209
- Virus, Varicella Zoster
 - Isolation and Characterization, Review, 79-4887

Drosophila

- Acetic Acid, (2,4,5-Trichlorophenoxy)-
 - Mutagenic Activity, Review, 79-4832

Drosophila melanogaster

- Neoplasms, Experimental
 - Adipose Tissue, 79-5282
 - Melanin, 79-5282

Drug Therapy

- Leukemia, Myeloblastic
 - Case Report, 79-4995
- Skin Neoplasms
 - Psoriasis, 79-5104
- Uterine Neoplasms
 - Estrogens, 79-5089
 - Progestational Hormones, 79-5089

Drug Therapy, Combination

- Leukemia, Myeloblastic
 - Hodgkin's Disease, 79-5103

Drugs

- Chemical Reactivity
 - Quantum Mechanics, Review, 79-4915
- Electronic Structure
 - Structure-Activity Relationship, Review, 79-4802

Dysgammaglobulinemia

- Casein
 - Antigen-Antibody Complex, 79-5240

Ear Neoplasms

- Hyperplasia
 - Case Report, Irrigation, 79-5313
 - Ethyl Alcohol, 79-5313
 - Isopropyl Alcohol, 79-5313

Endonucleases

- Virus, Epstein-Barr
 - DNA, Viral, 79-5160
- Virus, Herpes Simplex 1
 - DNA-RNA Hybridization, 79-5177
- Virus, Moloney Murine Leukemia
 - DNA, Viral, 79-5133
- Virus, Polyoma
 - DNA Replication, 79-5203

Endotoxins

- Bacillus thuringiensis*
 - Mutagenic Activity, Plants, 79-5027

Environmental Hazard

- Asbestos
 - Epidemiology, Review, 79-4811
- Carcinogen, Chemical
 - Dose-Response Study, Review, 79-4805
- Carcinogenic Metabolite
 - Epidemiology, Review, 79-4803
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Epidemiology, Review, 79-4811
- Genetics
 - Co-carcinogenic Effect, Review, 79-4909
- Mercury, Methyl-
 - Epidemiology, Review, 79-4811
- Mycotoxins
 - Epidemiology, Review, 79-4811
- Nitrosamines
 - Carcinogenic Potential, Review, 79-4836
- Polycyclic Hydrocarbons
 - Epidemiology, Review, 79-4811
- Zeolite
 - Epidemiology, Review, 79-4811

Eosinophils

- Graft vs Host Reaction
 - Bone Marrow, 79-5296
- Hematological Diseases
 - Bone Marrow, 79-5296
- Leukemia, Myeloblastic
 - Bone Marrow, 79-5296

Epidermal Growth Factor

- see Peptides

Epidermodysplasia Verruciformis

- Genetics
 - Case Report, 79-5172
- Virus, Papilloma
 - Antibodies, Viral, 79-5172
 - Genetics, 79-5172
 - Immunity, Cellular, 79-5172

Epoxide Hydratases

- Dieldrin
 - Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
 - 79-5068

Ergocryptine, 2-Bromo-

- Cervix Neoplasms

- Ergocryptine, 2-Bromo- (cont'd)**
 Carcinoma, Epidermoid, 79-5075
 Neoplasm Invasiveness, 79-5075
- Erythrocytes**
 Ethylene Glycol
 Howell-Jolly Bodies, 79-4957
 Ethylene Oxide
 Howell-Jolly Bodies, 79-4957
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 Chromosome Aberrations, 79-4996
 Mutagens
 Chromosome Aberrations, 79-4908
- Erythroleukemia**
 Azathioprine
 Case Report, Kidney Transplant, 79-5042
 Chromosome Abnormalities, 79-5042
 Butyric Acid, Sodium Salt
 Gangliosides, 79-4966
 Cholera Toxin
 Binding Sites, 79-4966
 Erythropoiesis
 Cells, Cultured, 79-5318
 Erythropoietin
 Colony Formation, 79-5318
 Virus, Friend Murine Leukemia
 DNA-RNA Hybridization, 79-5130
 Methanesulfonic Acid, Methyl Ester, 79-4952
- Erythropoiesis**
 Erythroleukemia
 Cells, Cultured, 79-5318
- Erythropoietin**
 Erythroleukemia
 Colony Formation, 79-5318
- Escherichia coli***
 Acetic Acid, (Ethylenedinitrilo)tetra-
 Lipopolysaccharides, 79-5092
 Antineoplastic Agents
 Mutagenic Metabolite, 79-5090
 Benzene, 4-Azido-1,3-dinitro-
 Mutagenic Activity, 79-5005
 Benzene, 4-Azido-1-Fluoro-2-nitro-
 Mutagenic Activity, 79-5005
 Propane, 1,2-Epoxy-
 Mutagenic Activity, 79-4964
 Stannane, Chlorotriethyl-
 Antibacterial Activity, 79-5092
 Stannane, Chlorotripropyl-
 Antibacterial Activity, 79-5092
 Stannane, Tributylchloro-
 Antibacterial Activity, 79-5092
- Esophageal Neoplasms**
 Carcinoma, Epidermoid
 Case Report, 79-5334
 Scleroderma, Systemic, 79-5333
 Ethyl Alcohol
 Epidemiology, 79-5356
 Epidemiology, France, 79-4924
 Epidemiology, Review, 79-4919
 Myoblastoma
 Case Report, 79-5332
 Nitrosamines
 Structure-Activity Relationship, Review, 79-4828
 Scleroderma, Systemic
 Case Report, 79-5333
- Esophageal Neoplasms (cont'd)**
 Smoking
 Epidemiology, France, 79-4924
 Epidemiology, Review, 79-4919
- Esophagus**
 Polyps
 Peutz-Jeghers Syndrome, 79-5305
- Estradiol**
 Aryl Hydrocarbon Hydroxylases
 Tissue Distribution, Rat, 79-5074
 Cells, Cultured
 DNA, Binding, 79-5085
 Cervix Neoplasms
 Adenocarcinoma, 79-5075
 Carcinoma, Epidermoid, 79-5075
 LS 1727
 Metabolism, 79-5046
 Microsomes
 DNA, Binding, 79-5085
 Prolactin
 Receptors, Hormone, 79-5047
 Serum Levels
 Ovariectomy, Hypophysectomy, 79-5051
 Uterus
 Receptors, Estrogen, 79-5087
- Estradiol, 17-Ethynyl-**
 Liver Neoplasms
 Adenoma, 79-5086
- Estrogenic Substances, Conjugated**
 Breast Neoplasms
 Epidemiology, 79-5354
 Cholelithiasis
 Drug Therapy, 79-5354
 Hysterectomy
 Drug Use Patterns, 79-5362
 Lipoproteins
 Drug Therapy, 79-5354
 Menopause
 Drug Use Patterns, 79-5362
 Uterine Neoplasms
 Epidemiology, 79-5362
- Estrogens**
 Breast Neoplasms
 Menopause, Review, 79-4928
 Risk Factors, Review, 79-4851
 Gynecologic Neoplasms
 Co-carcinogenic Effect, Review, 79-4929
 Liver Neoplasms
 Epidemiology, France, 79-5374
 Testicular Neoplasms
 Granulosa Cell Tumor, 79-4855
 Uterine Neoplasms
 Drug Therapy, 79-5089
 Epidemiology, 79-5383
 Epidemiology, Review, 79-4852, 79-4932
 Risk Factors, Review, 79-4851
- Estrone**
 Aryl Hydrocarbon Hydroxylases
 Tissue Distribution, Rat, 79-5074
 Carrier Proteins
 Cell Membrane, 79-4985
 Cholesterol
 Membranes, Binding, 79-4985
 Phosphatidylcholines

Estrone (cont'd)

- Membranes, Binding, 79-4985
- Serum Levels
 - Ovariectomy, Hypophysectomy, 79-5051
- Uterine Neoplasms
 - Epidemiology, 79-5383

Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-

- Chromosome Aberrations
 - Bone Marrow, 79-4960
 - Spermatzoa, 79-4960
- Nitrogen Monoxide
 - Carcinogenic, Teratogenic Potential, Rat, 79-4960
 - Chromosome Aberrations, 79-4960

Ethane, 1,2-Dichloro-

- Angiosarcoma
 - Carcinogenic Activity, Mouse, Rat, 79-4961
- Fibroma
 - Carcinogenic Activity, Mouse, Rat, 79-4961
- Mammary Neoplasms, Experimental
 - Adenocarcinoma, 79-4961
 - Carcinogenic Activity, Mouse, Rat, 79-4961
- Respiratory Tract Neoplasms
 - Carcinogenic Activity, Mouse, Rat, 79-4961
- Stomach Neoplasms
 - Carcinogenic Activity, Mouse, Rat, 79-4961
 - Carcinoma, Epidermoid, 79-4961
- Uterine Neoplasms
 - Carcinogenic Activity, Mouse, Rat, 79-4961

Ethane, 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)-

- Acetamide, *N*-Fluorene-2-yl-
 - Mutagenic Metabolite, 79-4963
- Iron
 - Metabolism, Rat, 79-5095

Ethanol, 2-Chloro-

- Chromosome Aberrations
 - Mutagenic Activity, 79-4957
- Mutagenic Activity
 - Plastics, Sterilized, 79-4957

Ether, Chloromethyl Methyl

- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813

Ether, Dichloromethyl Methyl

- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813

Ethidium Bromide

- Virus, Kirsten Murine Leukemia
 - Virus, Kirsten Murine Sarcoma, 79-5128
- Virus, Kirsten Murine Sarcoma
 - Cell Survival, 79-5128
- Virus, Murine Leukemia
 - Uridine, 2'-Deoxy-5-iodo-, 79-5128
 - Virus, Replication, 79-5128

Ethyl Alcohol

- Aryl Hydrocarbon Hydroxylases
 - Microsomes, Liver, 79-4956
- Benzo(a)pyrene
 - DNA, Binding, 79-4956
- 2*H*-1,4-Benzodiazepin-2-one, 1,3-Dihydro-7-nitro-5-phenyl-
 - Amino Derivatives, 79-5004
 - Metabolism, Liver, 79-5004
- Benzoic Acid, *p*-Nitro-
 - Alcohol Oxidoreductases, 79-5004

Ethyl Alcohol (cont'd)

- Metabolism, Liver, 79-5004
- Brain Neoplasms
 - Epidemiology, 79-5356
- Cytochrome P-450
 - Microsomes, Liver, 79-4956
- Ear Neoplasms
 - Hyperplasia, 79-5313
- Esophageal Neoplasms
 - Epidemiology, 79-5356
 - Epidemiology, France, 79-4924
 - Epidemiology, Review, 79-4919
- Ethylene, Chloro-
 - Metabolism, Liver, 79-4958
- Head and Neck Neoplasms
 - Neoplasms, Multiple Primary, 79-5355
- Hepatoma
 - Epidemiology, Review, 79-4919
- Laryngeal Neoplasms
 - Epidemiology, Review, 79-4919
- Liver Cirrhosis
 - Epidemiology, 79-5356
- Liver Neoplasms
 - Co-carcinogenic Activity, Review, 79-4836
- Nitrosamines
 - Fragmentation Products, Review, 79-4823
- Pharyngeal Neoplasms
 - Epidemiology, Review, 79-4919
- Respiratory Tract Neoplasms
 - Epidemiology, 79-5356
 - Epidemiology, France, 79-4924
- Smoking
 - Co-carcinogenic Effect, Review, 79-4919

Ethylene, Chloro-

- Adenosine Triphosphatase
 - Hepatocarcinogenesis, 79-4962
- Angiosarcoma
 - Carcinogenic Activity, Review, 79-4808
- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Mutagenic Activity, 79-4959
- Bone Neoplasms
 - Chondroma, 79-4808
- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813
- Chromosome Aberrations
 - Mutagenic Activity, Review, 79-4808
- Digestive System Neoplasms
 - Carcinogenic Activity, Review, 79-4808
- DNA
 - Carcinogenic Metabolite, Review, 79-4920
- Ethyl Alcohol
 - Metabolism, Liver, 79-4958
- Furan, Tetrahydro-
 - Metabolism, Liver, 79-4958
- Guanine, 8-Aza-
 - Mutation, 79-4959
- Mammary Neoplasms, Experimental
 - Carcinogenic Activity, Review, 79-4808
- Ouabain
 - Mutation, 79-4959
- Sebaceous Gland Neoplasms
 - Carcinogenic Activity, Review, 79-4808

Ethylene, Chloro- Polymer

- Angiosarcoma
 - Occupational Hazard, Review, 79-4808

- Ethylene, 1,1-Dichloro-**
Barbituric Acid, 5-Ethyl-5-phenyl-
Mutagenic Activity, 79-4959
- Ethylene, 1,1-Difluoro-**
Adenosine Triphosphatase
Hepatocarcinogenesis, 79-4962
- Ethylene Glycol**
Chromosome Aberrations
Mutagenic Activity, 79-4957
Erythrocytes
Howell-Jolly Bodies, 79-4957
- Ethylene Oxide**
Chromosome Aberrations
Mutagenic Activity, 79-4957
Mutagenic Activity, Review, 79-4809
Erythrocytes
Howell-Jolly Bodies, 79-4957
Leukemia
Carcinogenic Potential, Review, 79-4809
Mutagenic Activity
Plastics, Sterilized, 79-4957
Occupational Hazard
Epidemiology, Review, 79-4809
- Ethylene, Trichloro-**
Bladder Neoplasms
Occupational Hazard, 79-5376
DNA
Carcinogenic Metabolite, Review, 79-4920
Liver Neoplasms
Epidemiology, 79-5375
Occupational Hazard, 79-5376
Lung Neoplasms
Occupational Hazard, 79-5376
Mouth Neoplasms
Occupational Hazard, 79-5376
Occupational Hazard
Epidemiology, 79-5376
Rectal Neoplasms
Occupational Hazard, 79-5376
- Ethynodiol Diacetate**
Liver Neoplasms
Adenoma, 79-5086
- Extrachromosomal Inheritance**
Virus, Epstein-Barr
Virus Replication, Review, 79-4896
Virus, Polyoma
DNA, Viral, 79-5208
- Eye Neoplasms**
Immunosuppression
Surgery, Operative, Review, 79-4922
Melanoma
Epidemiology, Review, 79-4922
Neoplasm Metastasis
Surgery, Operative, Review, 79-4922
- Fetal Globulins**
Cell Transformation, Neoplastic
Enzymes, Review, 79-4899
Retrodifferentiation, Review, 79-4899
Liver Neoplasms
Acetamide, *N*-Fluorenyl-2-yl-, 79-4907
Aniline, *N,N*-Dimethyl-*p*-phenylazo-, 79-4907
- Fibrinolysis**
Adenocarcinoma
- Fibrinolysis (cont'd)**
Neoplasm Metastasis, 79-5307
Melanoma
Neoplasm Metastasis, 79-5307
- Fibroblasts**
Benz(a)anthracene, 7,12-Dimethyl-
Carcinogenic Metabolite, 79-5058
Benzo(a)pyrene
Carcinogenic Metabolite, 79-5058
DNA, Binding, 79-5061
Lymphocytes
Cell Adhesion, 79-5251
Malathion
Chromatids, 79-4971
Neoplasms, Experimental
Transplantation, Homologous, 79-5285
Virus, Avian Reticuloendotheliosis
Cell Transformation, Neoplastic, 79-5120
Virus, Polyoma
Transformation, Genetic, 79-5208
Virus, Rous Sarcoma
Glycoproteins, 79-5227
Succinate Dehydrogenase, 79-5227
- Fibroma**
Ethane, 1,2-Dichloro-
Carcinogenic Activity, Mouse, Rat, 79-4961
Nervous System Neoplasms
Ultrastructural Study, 79-5316
Ovarian Neoplasms
Epidemiology, 79-5380
Phosphoric Acid, Trimethyl Ester
Carcinogenic Activity, Mouse, Rat, 79-4816
Virus, Bovine Papilloma
DNA, Viral, 79-5156
- Fibronectins**
see Glycoproteins
- Fibrosarcoma**
Brain Neoplasms
Radiation, Ionizing, 79-5102
Cholanthrene, 3-Methyl-
Rat, Germfree, Review, 79-4918
Gastrointestinal Neoplasms
Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
79-4978
Hybrid Cells
Chromosomes, 79-5286
Tumorigenicity, Mouse, Nude, 79-5286
Lung Neoplasms
1,3-Butadiene, 2-Chloro-, 79-4967
Monocytes
Cell Aggregation, 79-5285
Neutrophils
Cell Aggregation, 79-5285
Photochemotherapy
Transplantation Immunology, 79-5099
Radiation, Ionizing
Aryl Hydrocarbon Hydroxylases, 79-5100
Transplantation, Homologous
Neoplasm Invasiveness, 79-5285
Virus, Herpes
Cells, Cultured, Review, 79-4870
Virus, Herpes Simplex 2
Neoplasm Transplantation, 79-5236
Temperature Sensitive Mutants, 79-5236

none, 3,3',4',5,7-Pentahydroxy-

- Guanine, 8-Aza-
Mutation, 79-5026
- Mutagenic Activity
Hamster V79 Cells, 79-5026

Fluoranthene

- Ames Test
Food Contamination, 79-5066
- Water Pollution
Quantitation Method, 79-5056

4-Nitro-2-amine

- Arylnitrenium Ions
Mutagenic Activity, 79-5038

4-Nitro-9-amine

- Arylnitrenium Ions
Mutagenic Activity, 79-5038

Food Additives

- Nitrous Acid, Sodium Salt
Risk Factors, Review, 79-4819

Food Contamination

- Aflatoxin B1
Milk, 79-5030
Weather, 79-5032
- Aflatoxin G1
Weather, 79-5032
- Aflatoxin G2
Weather, 79-5032
- Aflatoxin M1
Milk, 79-5030
- Benz(e)acephenanthrylene
Ames Test, 79-5066
- Benzo(g,h,i)perylene
Ames Test, 79-5066
- Coronene
Ames Test, 79-5066
- Fluoranthene
Ames Test, 79-5066
- Indeno(1,2,3-cd)pyrene
Ames Test, 79-5066
- Mycotoxins
Hepatotoxicity, 79-5031
- Nitrosamines
Animal Diet, Review, 79-4825
- Nitroso Compounds
Review, 79-4824
- Ochratoxin A
Body Fluids, Tissues, Cow, 79-5030
Milk, 79-5030
- Triphenylene
Ames Test, 79-5066
- Zearalenone
Body Fluids, Tissues, Cow, 79-5030

Formaldehyde

- Mutagenic Activity
Mammals, Microorganisms, Review, 79-4835
- Virus, SV40
Cell Membrane, 79-5220

Formamide, N-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

- Bladder Neoplasms
Carcinoma, 79-4864
Carcinoma, Papillary, 79-4993
Carcinoma, Transitional Cell, 79-4993
Neoplasm Metastasis, 79-4993
- DNA Repair

Formamide, N-(4-(5-Nitro-2-furyl)-2-thiazolyl)- (cont'd)

- Escherichia coli*, 79-5000
- Escherichia coli*
Mutagenic Activity, 79-5000
- Saccharomyces cerevisiae*
Mutagenic Activity, 79-5009

Freund's Adjuvant

- Virus, Marek's Disease Herpes
Transplantation Immunology, 79-5122

2-Furaldehyde, 5-Nitro-, Semicarbazone

- Escherichia coli*
Mutagenic Activity, 79-5000

Furan, Tetrahydro-

- Ethylene, Chloro-
Metabolism, Liver, 79-4958

Furoic Acid, 5-Nitro-

- Escherichia coli*
Mutagenic Activity, 79-5000

Fusarium moniliforme

- Mutagens
Ames Test, 79-5028
Isolation and Characterization, 79-5028

Gangliosides

- Erythroleukemia
Butyric Acid, Sodium Salt, 79-4966
- Melanoma
Metabolism, 79-5399

Gastrectomy

- Stomach Neoplasms
Adenocarcinoma, 79-5111
Diagnosis and Prognosis, 79-5111
Peptic Ulcer, 79-5111

Gastric Mucosa

- Stomach Neoplasms
Precancerous Conditions, 79-5378

Gastrin

- Pancreatic Neoplasms
Corticotropin, 79-5076

Gastrointestinal Hormones

- Pancreatic Neoplasms
Diarrhea, 79-5309
- Zollinger-Ellison Syndrome
Diarrhea, 79-5309

Gastrointestinal Neoplasms

- Apudoma
Classification, Review, 79-4912
- Concanavalin A
Lymphocyte Transformation, 79-5254
- Fibrosarcoma
Carbamic Acid, N-Methyl-N-nitroso-, Ethyl Ester
79-4978
- Leiomyosarcoma
Carbamic Acid, N-Methyl-N-nitroso-, Ethyl Ester
79-4978
- Plant Agglutinins
Lymphocyte Transformation, 79-5254
- Radiation, Ionizing
Epidemiology, 79-5385
Radiography, 79-5385
- Virus, Herpes Simplex
Antigen-Antibody Reactions, 79-5191

- Genetics**
- Environmental Hazard
 - Co-carcinogenic Effect, Review, 79-4909
 - Epidermodysplasia Verruciformis
 - Case Report, 79-5172
 - Virus, Papilloma, 79-5172
 - Heavy Chain Disease
 - Hypersensitivity, Delayed, 79-5252
 - B-Lymphocytes, 79-5252
 - Hodgkin's Disease
 - Histocompatibility Antigens, 79-5295
 - Leukemia, Lymphoblastic
 - Autoimmune Diseases, 79-5267
 - Precancerous Conditions, 79-5289
 - Leukemia, Myeloblastic
 - Autoimmune Diseases, 79-5267
 - Precancerous Conditions, 79-5289
 - Melanoma
 - Killer Cells, 79-5275
 - RH-HR Blood-Group System, 79-5275
 - Ovarian Neoplasms
 - Case Report, 79-5347
 - Cystadenocarcinoma, 79-5347
 - Pheochromocytoma
 - Case Report, 79-5308
 - Hypertension, 79-5308
 - Teratoid Tumor
 - Chloramphenicol, 79-5391
 - Hypoxanthine Phosphoribosyltransferase, 79-5391
 - Virus, Herpes Simplex 1
 - Immune Response, Mouse, 79-5182
 - Virus, Murine Leukemia
 - Virus Replication, 79-5127
 - X-Tropic NZB Virus, 79-5127
- Gentamicin**
- Aminoglycosides
 - Ames Test, 79-5012
- Glioblastoma Multiforme**
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - DNA Repair, 79-5200
 - Virus, Adeno 5
 - Virus Activation, 79-5200
- Glioma**
- Cell Survival
 - Embryonic Tissue, 79-4979
 - Urea, Ethyl Nitroso-
 - Transplantation, Heterologous, 79-4979
- Glomus Jugulare Tumor**
- see Paraganglioma, Nonchromaffin
- D-Gluconic Acid, Strontium Salt**
- Calcium
 - Serum Levels, 79-4951
 - Strontium
 - Serum Levels, 79-4951
- Glucose, 2-Deoxy-**
- Insulin
 - Metabolism, 79-5077
 - Peptides
 - Metabolism, 79-5077
 - Phorbol Esters
 - Metabolism, 79-5077
 - 12-O-Tetradecanoylphorbol-13-acetate
 - Metabolism, 79-5077
- Glucosephosphate Dehydrogenase**
- HeLa Cells
 - Hybrid Cells, 79-5286
- Glucosphosphatase**
- Cycloheximide
 - Microsomes, Liver, 79-4969
- Glucuronidase**
- Bladder Neoplasms
 - Carcinogen, Chemical, 79-4846
 - Carcinogen, Environmental, 79-4846
 - Cell Division, 79-4846
- Glutaraldehyde**
- Virus, Marek's Disease Herpes
 - Transplantation Immunology, 79-5122
- Glutathione**
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 - Metabolism, Rat, 79-5021
 - Toluene-2,4-diamine
 - Proteins, Binding, 79-5022
- Glutathione Peroxidase**
- Smoking
 - Macrophages, 79-5015
- Glutathione Transferases**
- Carcinogen, Chemical
 - Metabolism, Review, 79-4841
- Glycerophosphate Dehydrogenase**
- Urea, Ethyl Nitroso-
 - Trigeminal Nerve, Rat, 79-5071
- Glycine, *N,N*-Bis(carboxymethyl)-**
- Hematuria
 - Dose-Response Study, Rat, 79-4983
- Glycine, *N,N*-Bis(carboxymethyl)-, Trisodium Salt, Monohydrate**
- Hydronephrosis
 - Strain Difference, Rat, 79-4983
- Glycogenosis**
- Urea, Ethyl Nitroso-
 - Liver, Mouse, 79-4981
- Glycolipids**
- Teratoid Tumor
 - Antigens, Neoplasm, 79-5262
- Glycoproteins**
- Cell Transformation, Neoplastic
 - Cell Membrane, 79-5261
 - Colony Formation, 79-5261
 - Hematopoietic Stem Cells
 - Cell Membrane, 79-5164
 - Neoplasms, Experimental
 - Mouse, Nude, 79-5261
 - Teratoid Tumor
 - Antigens, Neoplasm, 79-5262
 - Virus, Epstein-Barr
 - Cell Membrane, 79-5164
 - Hematopoietic Stem Cells, 79-5164
 - Virus, Friend Spleen Focus-Forming
 - Antigenic Determinants, 79-5131
 - Virus, Herpes
 - Cell Fusion, Review, 79-4876
 - Cell Membrane, Review, 79-4869
 - Virus, Mink Cell Focus-Inducing
 - Antigenic Determinants, 79-5131

Glycoproteins (cont'd)

- Virus, Rauscher Murine Leukemia
 - Cell Transformation, Neoplastic, 79-5137
 - Lymphoid Tissue, Binding, 79-5137
- Virus, Rous Sarcoma
 - Antigenic Determinants, 79-5116
 - Fibroblasts, 79-5227
 - Tunicamycin, 79-5116
- Virus, Sendai
 - Cell Membrane, 79-5229
 - Hemagglutination, 79-5229
 - Neuraminidase, 79-5229
- Virus, SV40
 - Cell Transformation, Neoplastic, 79-5220
- Virus, Vesicular Stomatitis
 - Cell Fusion, 79-5232

Gold

- Lung Neoplasms
 - Pinocytosis, 79-5257

Gonadotropins

- Benz(a)anthracene, 7,12-Dimethyl-
 - Serum Levels, 79-5050
- Testicular Neoplasms
 - Choriocarcinoma, 79-4855
 - Disgerminoma, 79-4855
 - Granulosa Cell Tumor, 79-4855
 - Leydig Cell Tumor, 79-4855
 - Teratoid Tumor, 79-4855

Gonadotropins, Chorionic

- Choriocarcinoma
 - Endocrine Abnormalities, Review, 79-4850
- Neoplasms
 - Endocrine Abnormalities, Review, 79-4850
- Ovarian Neoplasms
 - Endocrine Abnormalities, Review, 79-4850
- Testicular Neoplasms
 - Endocrine Abnormalities, Review, 79-4850

Graft vs Host Reaction

- Eosinophils
 - Bone Marrow, 79-5296
- T-Lymphocytes
 - Histocompatibility Antigens, 79-5245
- Macrophages
 - Bone Marrow, 79-5296

Graft Rejection

- Bone Marrow
 - Immune Response, Mouse, 79-5182
- Carcinoma, Basal Cell
 - Necrosis, 79-5271
- Histamine
 - Immune Response, Review, 79-4842
- T-Lymphocytes
 - Histocompatibility Antigens, 79-5245
- Prostaglandins
 - Adenosine Cyclic 3',5' Monophosphate, 79-4842
 - Guanosine Cyclic 3',5' Monophosphate, 79-4842
 - Immune Response, Review, 79-4842
- Virus, Herpes Simplex 1
 - Immune Response, Mouse, 79-5182

Graft Survival

- Lymphocyte Depletion
 - Rat, Nude, 79-5259

Granular Cell Tumor

see Myoblastoma

Granulocytes

- Leukemia, Myeloblastic
 - Colony Formation, 79-5291
 - Precancerous Conditions, 79-5291
- Lung Neoplasms
 - Colony Stimulating Factor, 79-5326

Granuloma

- Lung Neoplasms
 - Neoplasm Metastasis, 79-5278
 - Neoplasm Regression, Spontaneous, 79-5278

Granulosa Cell Tumor

- Ovarian Neoplasms
 - Epidemiology, 79-5380
 - Puberty, Precocious, 79-5346
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Testicular Neoplasms
 - Estrogens, 79-4855
 - Gonadotropins, 79-4855

Growth

- Carcinoma, Ehrlich Tumor
 - Selenic Acid, Dipotassium Salt, 79-4950
 - Selenious Acid, Disodium Salt, 79-4950
 - Selenium Dioxide, 79-4950
- Mammary Neoplasms, Experimental
 - LS 1727, 79-5046
- Melanoma
 - Lipids, 79-5399

Guanidine, 1-Methyl-3-nitro-1-nitroso-

- Ames Test
 - Dose-Response Study, 79-5059
- Astrocytoma
 - DNA Repair, 79-5200
- Cell Differentiation
 - Epithelium, 79-5002
- Glioblastoma Multiforme
 - DNA Repair, 79-5200
- Keratin
 - Forestomach, Rat, 79-5002
- Methanesulfonic Acid, Ethyl Ester
 - Co-mutagenic Activity, 79-5059
- Neoplasms
 - DNA Repair, 79-5200
- Stomach Neoplasms
 - Carcinoma, 79-5001
 - Histological Study, Mouse, 79-5001
 - Hyperplasia, 79-5001
 - Polyps, 79-5001
- Virus, Adeno 5
 - DNA Repair, 79-5200

Guanine, 8-Aza-

- Ethylene, Chloro-
 - Mutation, 79-4959
- Flavone, 3,3',4',5,7-Pentahydroxy-
 - Mutation, 79-5026
- Kaempferol
 - Mutation, 79-5026

Guanosine Cyclic 3',5' Monophosphate

- Carcinogen, Chemical
 - Metabolism, Review, 79-4937
- Neoplasms, Experimental
 - Growth, Review, 79-4937
- Prostaglandins

- Guanosine Cyclic 3',5' Monophosphate (cont'd)**
Graft Rejection, 79-4842
- Gynecologic Neoplasms**
Contraceptives, Oral
Epidemiology, Review, 79-4931
Estrogens
Co-carcinogenic Effect, Review, 79-4929
4,4'-Stilbenediol, α,α' -Diethyl-
Epidemiology, Review, 79-4931
- Gynecomastia**
Digitalis
Structure-Activity Relationship, Review, 79-4848
Testicular Neoplasms
Endocrine Abnormalities, Review, 79-4855
- Head and Neck Neoplasms**
Carcinoma, Epidermoid
Case Report, 79-5311
Neoplasm Metastasis, 79-5311
Neoplasms, Multiple Primary
Epidemiology, 79-5355
Ethyl Alcohol, 79-5355
Smoking, 79-5355
Virus, Epstein-Barr
Antibodies, Viral, 79-5166
- Heart Neoplasms**
Sarcoma
Case Report, 79-5320
Heart Enlargement, 79-5320
- Heavy Chain Disease**
Genetics
Hypersensitivity, Delayed, 79-5252
B-Lymphocytes, 79-5252
Immunoglobulins, Alpha Chain
B-Lymphocytes, 79-5252
T-Lymphocytes, 79-5252
B-Lymphocytes
IgA, 79-5252
Lymphoma
Immunoglobulins, Alpha Chain, 79-5252
- HeLa Cells**
Cholera Toxin
Binding Sites, 79-4966
Hybrid Cells
Glucosephosphate Dehydrogenase, 79-5286
Tumorigenicity, Mouse, Nude, 79-5286
- Hemagglutination**
Virus, Sendai
Glycoproteins, 79-5229
- Hemangioendothelioma**
Liver Neoplasms
Thorium Dioxide, 79-5110
- Hemangioma**
Liver Neoplasms
12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Hematological Diseases**
Eosinophils
Bone Marrow, 79-5296
Leukemia
Precancerous Conditions, 79-5289
Macrophages
Bone Marrow, 79-5296
- Hematopoietic Stem Cells**
Glycoproteins
Cell Membrane, 79-5164
Virus, Epstein-Barr
Glycoproteins, 79-5164
- Hematuria**
Glycine, *N,N*-Bis(carboxymethyl)-
Dose-Response Study, Rat, 79-4983
- Hemocytes**
Adipose Tissue
Phagocytosis, 79-5282
Neoplasms, Experimental
Cell Aggregation, 79-5282
Phagocytosis, 79-5282
- Hemolysins**
Virus, Herpes Simplex 1
Complement, 79-5185
Virus, Measles
Antibodies, Viral, 79-5228
- Hepatitis**
Virus, Herpes Simplex 1
Cytopathogenic Effects, *Tupaia*, 79-5192
Virus, Herpes Simplex 2
Cytopathogenic Effects, *Tupaia*, 79-5192
- Hepatoma**
Aflatoxin B1
Portocaval Shunt, 79-5034
Alpha 1-Antitrypsin
Immunocytochemical Study, 79-5330
Androgens
Histological Study, Review, 79-4847
Barbituric Acid, 5-Ethyl-5-phenyl-
DNA Replication, 79-5057
Benzenamine, 4,4'-Methylenebis(2-chloro)-
Dose-Response Study, Rat, 79-5024
Benzo(a)pyrene
DNA Replication, 79-5057
Brain
Neoplasm Metastasis, 79-5109
Carcinogen, Chemical
Air Pollutants, 79-5019
Child
Epidemiology, Review, 79-4925
Contraceptives, Oral
Co-carcinogenic Effect, Review, 79-4929
Cycloheximide
DNA Replication, 79-5057
Diet
Restriction, 79-5397
Ethyl Alcohol
Epidemiology, Review, 79-4919
Oxymetholone
Histological Study, Review, 79-4847
Propane, 2-Nitro-
Inhalation Study, Rat, 79-4976
Testosterone
Histological Study, Review, 79-4847
12-O-Tetradecanoylphorbol-13-acetate
Mouse, Nude, 79-5041
Urea, Ethyl Nitroso-
Transplacental Carcinogenesis, 79-4981
Urea, Methyl Nitroso-
DNA Replication, 79-5057
Virus, Hepatitis B
Epidemiology, Review, 79-4898

- Hepatoma (cont'd)**
 Wounds and Injuries
 Neoplasm Metastasis, 79-5109
- Hereditary Diseases**
 Thyroid Neoplasms
 Carcinoma, 79-5299
- Herpes Zoster**
 DNA, Viral
 Isolation and Characterization, Review, 79-4887
- Hippel-Lindau Disease**
 Pancreatic Neoplasms
 Angioma, 79-5303
 Case Report, 79-5303
 Cystadenoma, 79-5303
 Sprue
 Pancreatic Insufficiency, 79-5303
- Histamine**
 Graft Rejection
 Immune Response, Review, 79-4842
 4,4'-Stilbenediol, α,α' -Diethyl-
 Amide Derivative, 79-5081
- Histiocytosis X**
 Reticuloendotheliosis
 Case Report, Infant, 79-5284
- Histocompatibility Antigens**
 Adenocarcinoma
 Leukocytes, 79-5246
 Transplantation Immunology, 79-5246
 Virus, Herpes Simplex 1, 79-5184
 Anemia, Aplastic
 Child, 79-5247
 Parental Compatibility, 79-5247
 Bladder Neoplasms
 1-Butanol, 4-(Butylnitrosamino)-, 79-4992
 Transplantation Immunology, 79-4992
 Carcinoma, Transitional Cell
 Phenotype, 79-5283
 Hodgkin's Disease
 Antigen Frequency, 79-5295
 Genetics, 79-5295
 Hypersensitivity, Delayed
 Antigenic Determinants, 79-5245
 Immunity, Cellular, Review, 79-4902
 Leukemia
 Child, 79-5247
 Parental Compatibility, 79-5247
 Leukemia, Lymphocytic
 Immunologic Deficiency Syndromes, 79-5290
 B-Lymphocytes
 Transplantation Immunology, 79-5246
 T-Lymphocytes
 Graft vs Host Reaction, 79-5245
 Graft Rejection, 79-5245
 Immune Response, Review, 79-4902
 Immunity, Cellular, 79-5244
 Killer Cells, 79-5244
 Lymphocyte Cooperation, Review, 79-4902
 Lymphoma
 Antigen-Antibody Reactions, 79-5270
 Cell Membrane, 79-5270
 Virus, Marek's Disease Herpes, 79-5121
 Lymphosarcoma
 Immunologic Deficiency Syndromes, 79-5290
 Macrophages
- Histocompatibility Antigens (cont'd)**
 Transplantation Immunology, 79-5246
 Mammary Neoplasms, Experimental
 Hybrid Cells, 79-5279
 Melanoma
 Antigenic Determinants, 79-5276
 Metabolism, Inborn Errors
 Cortisol, 79-5306
 Oncogenic Viruses
 Immunity, Cellular, Review, 79-4902
 Plasmacytoma
 Cell Differentiation, 79-5264
 RNA
 Immunity, Cellular, 79-5234
 Sarcoma
 Cholanthrene, 3-Methyl-, 79-5248
 Neoplasm Transplantation, 79-5248
 Sarcoma, Mast Cell
 Killer Cells, 79-5244
 Skin Neoplasms
 Psoriasis, 79-5277
 Testicular Neoplasms
 Neoplasm Metastasis, 79-5249
 Teratoid Tumor, 79-5249
 Virus, Herpes Simplex 1
 Neoplasm Metastasis, 79-5184
 Transplantation Immunology, 79-5184
 Virus, Marek's Disease Herpes
 Genetic Resistance, 79-5121
 Transplantation Immunology, 79-5121
 Virus, SV40
 Interferon, 79-5217
- Hodgkin's Disease**
 Concanavalin A
 Binding Sites, Review, 79-4905
 Eosinophils
 Bone Marrow, 79-5296
 Histocompatibility Antigens
 Antigen Frequency, 79-5295
 Genetics, 79-5295
 Immunologic Deficiency Syndromes
 Agammaglobulinemia, 79-5266
 Leukemia
 Immunosuppression, Review, 79-4906
 Leukemia, Myeloblastic
 Case Report, 79-5103
 Drug Therapy, Combination, 79-5103
 Radiotherapy, 79-5103
 Lymphocytes
 Concanavalin A, 79-4905
 B-Lymphocytes
 Lymphocyte Transformation, 79-5294
 Macrophages
 Bone Marrow, 79-5296
 Neoplasms, Multiple Primary
 Immunohistological Study, 79-5294
 Immunosuppression, Review, 79-4906
 Sarcoma, Kaposi's
 Immunosuppression, Review, 79-4906
 Stomach Neoplasms
 Epidemiology, 79-5377
 Thyroid Neoplasms
 Immunosuppression, Review, 79-4906
 Virus, Epstein-Barr
 Antigens, Viral, 79-5171
 Virus, Herpes Simplex
 Antigen-Antibody Reactions, 79-5191

- Homocysteine, S-Adenosyl-**
Neuroblastoma
Adenine, 79-5393
- Homocysteine, S-Tubercidinyl-**
Neuroblastoma
Metabolism, 79-5393
- Hordeum vulgare**
1,3-Benzenedicarbonitrile, 2,4,5,6-Tetrachloro-
Chromosome Aberrations, 79-4972
Crotonic Acid, 3-Hydroxy-, Methyl Ester, Dimethyl
Phosphate
Chromosome Aberrations, 79-4972
Urea, 3-(*p*-Chlorophenyl)-1,1-dimethyl-
Chromosome Aberrations, 79-4972
- Hormones**
Cell Division
Hepatocytes, Review, 79-4938
- Hybrid Cells**
Fibrosarcoma
Chromosomes, 79-5286
Tumorigenicity, Mouse, Nude, 79-5286
HeLa Cells
Glucosephosphate Dehydrogenase, 79-5286
Tumorigenicity, Mouse, Nude, 79-5286
Mammary Neoplasms, Experimental
Antigens, Neoplasm, 79-5279
Histocompatibility Antigens, 79-5279
L Cells, 79-5279
Melanoma
Antibody Specificity, 79-5263
Plasmacytoma, 79-5263
- Hydantoin, 5,5-Diphenyl-**
Transplacental Carcinogenesis
Epidemiology, Review, 79-4815
- Hydantoin, 1-((5-Nitrofurfurylidene)amino)-**
Escherichia coli
Mutagenic Activity, 79-5000
Nitroso Compounds
Drug Contamination, 79-5010
Saccharomyces cerevisiae
Mutagenic Activity, 79-5009
Urine
Mutagenic Activity, 79-5009
- Hydatidiform Mole**
Choriocarcinoma
Karyotyping, 79-5350
Neoplasm Metastasis, 79-5350
Uterine Neoplasms
Choriocarcinoma, 79-5350
Karyotyping, 79-5350
- Hydrazine**
Mutagenic Activity
Mammals, Microorganisms, Review, 79-4835
- Hydrazine, 1,2-Dimethyl-**
5 β -Cholan-24-oic Acid, 3 α ,7 α -Dihydroxy-
Co-carcinogenic Effect, 79-4977
Colonic Neoplasms
Adenocarcinoma, 79-4977
Adenoma, 79-4977
5 β -Cholan-24-oic Acid, 3 α ,7 α -Dihydroxy-, 79-4977
- Hydrazones**
Structure-Activity Relationship
- Hydrazones (cont'd)**
Electronic Delocalization, 79-4987
- Hydrocarbons, Chlorinated**
Environmental Pollutants
Quantitation Method, Review, 79-4837
- Hydrogen Peroxide**
Smoking
Phagocytosis, 79-5015
- Hydronephrosis**
Glycine, *N,N*-Bis(carboxymethyl)-, Trisodium Salt,
Monohydrate
Strain Difference, Rat, 79-4983
- Hydroxylamine**
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 79-5049
Hyperplasia, 79-5049
- Hydroxylases**
Progesterone
Adrenal Cortex, Rat, 79-5073
- 6-Hydroxymethylbenzo(a)pyrene**
see Benzo(a)pyrene-6-methanol
- Hypercalcemia**
Disgerminoma
Endocrine Abnormalities, Review, 79-4855
Melanoma
Case Report, 79-5324
Neoplasm Metastasis, 79-5324
- Hyperparathyroidism**
Melanoma
Neoplasm Metastasis, 79-5324
Parathyroid Hormone, 79-5324
Thyroid Neoplasms
Carcinoma, 79-5300
Case Report, 79-5300
- Hyperplasia**
Ear Neoplasms
Case Report, Irrigation, 79-5313
Ethyl Alcohol, 79-5313
Isopropyl Alcohol, 79-5313
Lymphoid Tissue
Leukemia, 79-5149
Mammary Neoplasms, Experimental
Hydroxylamine, 79-5049
Ribosomes
Epidermis, Review, 79-4910
Skin Neoplasms
Virus, Herpes, 79-4881
Stomach Neoplasms
Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
Thyroid Neoplasms
Calcitonin, 79-5300
Virus, Guinea Pig RNA Tumor
Viral Interactions, 79-5149
- Hypersensitivity**
Virus, Pox
Immunization, Review, 79-4897
- Hypersensitivity, Delayed**
Burkitt's Lymphoma
Virus, Epstein-Barr, 79-5167
Heavy Chain Disease
Genetics, 79-5252

Hypersensitivity, Delayed (cont'd)

- Histocompatibility Antigens
 - Antigenic Determinants, 79-5245
 - Immunity, Cellular, Review, 79-4902
- Keratoacanthoma
 - Neoplasm Regression, Spontaneous, 79-5045
- RNA
 - Immunity, Cellular, 79-5234
- Urogenital Neoplasms
 - Neoplasms, Multiple Primary, 79-5281
- Virus, Epstein-Barr
 - Antibodies, Viral, 79-5167
- Virus, Herpes Simplex 2
 - Antibodies, 79-5194
- Virus, Marek's Disease Herpes
 - Corynebacterium parvum*, 79-5125

Hypertension

- Pheochromocytoma
 - Genetics, 79-5308
- Uterine Neoplasms
 - Epidemiology, Review, 79-4933

Hyperthyroidism

- Leukemia, Lymphoblastic
 - Autoimmune Diseases, 79-5267
- Teratoid Tumor
 - Endocrine Abnormalities, Review, 79-4855
- Thyroid Neoplasms
 - Adenoma, 79-5301
 - Plummer's Disease, 79-5301

Hypoxanthine Phosphoribosyltransferase

- Teratoid Tumor
 - Genetics, 79-5391

IgA

- Heavy Chain Disease
 - B-Lymphocytes, 79-5252
- Immunologic Deficiency Syndromes
 - Antigen-Antibody Complex, 79-5240
- Nasopharyngeal Neoplasms
 - Virus, Epstein-Barr, 79-5166
- Plasmacytoma
 - Immunoglobulins, Surface, 79-5264
- Sarcoma, Reticulum Cell
 - Cyroglobulins, 79-5272
 - Rheumatoid Factor, 79-5272

IgG

- Agammaglobulinemia
 - Case Report, Child, 79-5266
- Burkitt's Lymphoma
 - Antigen-Antibody Complex, 79-5165
- Colonic Neoplasms
 - Antigen-Antibody Complex, 79-5239
- Melanoma
 - Antigen-Antibody Complex, 79-5239
- Sarcoma, Reticulum Cell
 - Cellular Inclusions, 79-5297
 - Cyroglobulins, 79-5272
 - Ribonucleoproteins, 79-5297
- Virus, Herpes Lucke
 - Antibody Formation, 79-5126
 - Cell Differentiation, 79-5126
- Virus, Herpes Simplex 1
 - Anti-Antibodies, 79-5183

IgM

- Leucosarcoma

IgM (cont'd)

- Immunoglobulins, Surface, 79-5268
- Leukemia
 - B-Lymphocytes, 79-4900
- Multiple Myeloma
 - B-Lymphocytes, 79-4900
- Neoplasms, Experimental
 - Autoantibodies, 79-5274
- Plasmacytoma
 - Binding Sites, 79-5265
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
 - Chromosome Aberrations
 - Micronucleus Test, 79-4996
 - Erythrocytes
 - Chromosome Aberrations, 79-4996
 - Lymphocytes
 - Chromosome Aberrations, 79-4996
- 2-Imidazolidinethione
 - Bladder Neoplasms
 - Carcinogenic Potential, Review, 79-4833
 - Occupational Hazard
 - Epidemiology, Review, 79-4833
- Imipramine Hydrochloride
 - Nitroso Compounds
 - Drug Contamination, 79-5010
- Immune Serums
 - Complement
 - Strain Difference, Rabbit, 79-5237
 - Infectious Mononucleosis
 - Lymphocyte Transformation, 79-5170
 - Lymphosarcoma
 - Complement, 79-5237
 - Virus, Herpes Simplex 1
 - Cell Membrane Permeability, 79-5185
 - Lactate Dehydrogenase, 79-5183
 - Proteins, 79-5183
- Immunity, Cellular
 - Antigens
 - RNA, 79-5234
 - Bladder Neoplasms
 - Antigenic Determinants, 79-4992
 - Epidermodysplasia Verruciformis
 - Virus, Papilloma, 79-5172
 - Histocompatibility Antigens
 - RNA, 79-5234
 - Hypersensitivity, Delayed
 - RNA, 79-5234
 - Infectious Mononucleosis
 - Virus, Epstein-Barr, 79-5170
 - Keratoacanthoma
 - Neoplasm Regression, Spontaneous, 79-5045
 - T-Lymphocytes
 - Histocompatibility Antigens, 79-5244
 - Lymphoma
 - Interferon, 79-5159
 - Lymphocyte Transformation, 79-5159
 - Virus, Marek's Disease Herpes, 79-5122
 - Neoplasms, Experimental
 - Gene, Yellow, 79-5260
 - Neuroblastoma
 - Lymphocyte Culture Test, Mixed, 79-5255
 - RNA
 - Lymphokines, 79-5234
 - Virus, Herpes Simplex 1
 - Lymphocyte Transformation, 79-5181

- Immunity, Cellular (cont'd)**
 - Macrophages, 79-5181
 - Virus, Herpes Simplex 2
 - T-Lymphocytes, 79-5194
 - Macrophages, 79-5194
 - Systemic, Vaginal Infections, 79-5194
 - Virus, Marek's Disease Herpes
 - Antigens, 79-5122
 - Virus, Turkey Herpes, 79-5125
- Immunization**
 - Cholanthrene, 3-Methyl-
 - Antigen-Antibody Reactions, 79-5054
 - Neoplasms, Experimental
 - Cholanthrene, 3-Methyl-, 79-5054
 - Virus, Herpes Simplex 1
 - Neoplasm Metastasis, 79-5184
 - Virus, Marek's Disease Herpes
 - Tumor-Cell Vaccines, 79-5125
- Immunoglobulins, Alpha Chain**
 - Heavy Chain Disease
 - B-Lymphocytes, 79-5252
 - T-Lymphocytes, 79-5252
 - Lymphoma
 - Heavy Chain Disease, 79-5252
- Immunoglobulins, Heavy Chain**
 - Myeloma Proteins
 - Amino Acids, 79-5238
 - Plasmacytoma
 - Amino Acids, 79-5265
 - Carbohydrates, 79-5265
- Immunoglobulins, Light Chain**
 - Sarcoma, Reticulum Cell
 - Cellular Inclusions, 79-5297
- Immunoglobulins, Surface**
 - Leucosarcoma
 - IgM, 79-5268
 - Plasmacytoma
 - Cell Differentiation, 79-5264
 - IgA, 79-5264
- Immunologic Deficiency Syndromes**
 - Carcinoma, Epidermoid
 - B-Lymphocytes, 79-5290
 - Hodgkin's Disease
 - Agammaglobulinemia, 79-5266
 - IgA
 - Antigen-Antibody Complex, 79-5240
 - Leukemia, Lymphocytic
 - Case Report, 79-5290
 - Histocompatibility Antigens, 79-5290
 - B-Lymphocytes, 79-5290
 - Lymphosarcoma
 - Histocompatibility Antigens, 79-5290
 - B-Lymphocytes, 79-5290
 - Milk Proteins
 - Antigen-Antibody Complex, 79-5240
- Immunosuppression**
 - Breast Neoplasms
 - Pregnancy, 79-5360
 - Eye Neoplasms
 - Surgery, Operative, Review, 79-4922
 - Kidney Neoplasms
 - Cachexia, 79-5280
 - Papilloma
 - Antilymphocyte Serum, 79-5256
- Immunosuppression (cont'd)**
 - Psoralen, 8-Methoxy-
 - T-Lymphocytes, 79-5099
 - Sarcoma
 - Cholanthrene, 3-Methyl-, 79-5053
 - Sarcoma, Mast Cell
 - Antigen-Antibody Reactions, 79-5273
 - Radiation, Ionizing, 79-5273
 - Ultraviolet Rays, 79-5273
 - Ultraviolet Rays
 - T-Lymphocytes, 79-5099
 - Virus, Cytomegalo
 - Virus Replication, 79-5158
 - Virus, Herpes Simplex 1
 - T-Lymphocytes, 79-5182
 - Macrophages, 79-5182
 - Radiation, Ionizing, 79-5182
 - Virus, Herpes Simplex 2
 - Neoplasm Transplantation, 79-5236
- Indeno(1,2,3-cd)pyrene**
 - Ames Test
 - Food Contamination, 79-5066
 - Water Pollution
 - Quantitation Method, 79-5056
- Infectious Mononucleosis**
 - Immune Serums
 - Lymphocyte Transformation, 79-5170
 - Phosphonoacetic Acid
 - Virus Replication, 79-5168
 - Plant Agglutinins
 - Lymphocyte Transformation, 79-5170
 - Virus, Epstein-Barr
 - Antibodies, Viral, 79-5166
 - Antigens, Viral, 79-5171
 - DNA-RNA Hybridization, 79-5169
 - Epidemiology, Review, 79-4894
 - Epithelial Cells, 79-5169
 - Immune Response, Review, 79-4895
 - Immunity, Cellular, 79-5170
 - Leukocytes, 79-5168
 - Lymphocyte Transformation, Review, 79-4895
 - Molecular Biology, Review, 79-4896
 - Saliva, 79-5166
- Insulin**
 - Glucose, 2-Deoxy-
 - Metabolism, 79-5077
 - Virus, Harvey Murine Sarcoma
 - Cell Differentiation, 79-5144
 - Virus, Kirsten Murine Sarcoma
 - Cell Differentiation, 79-5144
 - Virus, Moloney Murine Sarcoma
 - Cell Differentiation, 79-5144
- Interferon**
 - Lymphoma
 - Immunity, Cellular, 79-5159
 - Virus, Varicella-Zoster, 79-5159
 - Virus, Herpes Simplex 1
 - Anti-Antibodies, 79-5173
 - Immune Response, Mouse, 79-5173
 - Virus Replication, 79-5241
 - Virus, Murine Sarcoma-Leukemia
 - Cell Transformation, Neoplastic, 79-5129
 - Clone Cells, 79-5129
 - Virus, SV40
 - Antigens, Neoplasm, 79-5217

Interferon (cont'd)

- Histocompatibility Antigens, 79-5217
- Virus, Vesicular Stomatitis
- RNA, Messenger, 79-5227

Intestinal Neoplasms

- Adenocarcinoma
 - Bracken Fern, 79-5035
 - Neoplasm Transplantation, 79-5035
 - Polyps, 79-4913
- Adenocarcinoma, Papillary
 - Methane, Azoxy-, 79-4955
- Bacteria
 - Co-carcinogenic Effect, Review, 79-4918
- Carcinoid Tumor
 - Case Report, 79-5337
 - Neoplasm Metastasis, 79-5337
 - Neoplasms, Multiple Primary, 79-5337
- Carcinoma, Mucinous
 - Methane, Azoxy-, 79-4955
- Dietary Fats
 - Epidemiology, Review, 79-4913
- Metaplasia
 - Carrageen, 79-5036
- Methane, Azoxy-
 - Pancreaticobiliary Diversion, 79-4955
- Neoplasm Transplantation
 - Ileal Tumor, 79-5035
- Polyps
 - Precancerous Conditions, Review, 79-4913

Iron

- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Metabolism, Rat, 79-5095
- p*-Dioxane
 - Metabolism, Rat, 79-5095
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 - Metabolism, Rat, 79-5095
- Tobacco
 - Heavy Metal Levels, 79-4944

Iron Oxide

- Adenoma
 - Dibenz(a,h)acridine, 79-4947
- Dibenz(a,h)acridine
 - Co-carcinogenic Effect, Hamster, 79-4947
- Lymphoma
 - Dibenz(a,h)acridine, 79-4947
- Papilloma
 - Dibenz(a,h)acridine, 79-4947
- Respiratory Tract Neoplasms
 - Benzo(a)pyrene, 79-4947
 - Dibenz(a,h)acridine, 79-4947

Islet Cell Tumor

- Pancreatic Neoplasms
 - Adenomatosis, Familial Endocrine, 79-5309

Isoantigens

- Uterine Neoplasms
 - Carcinoma, 79-5243
 - Isolation and Characterization, 79-5243

Isopropyl Alcohol

- Ear Neoplasms
 - Hyperplasia, 79-5313

Isoproterenol

- Astrocytoma
 - Adenosine Cyclic 3',5' Monophosphate, 79-5072
 - Adenyl Cyclase, 79-5072

Isoproterenol (cont'd)

- Receptors, Adrenergic, 79-5072

Isosafrole

- see Benzene, 1,2-(Methylenedioxy)-4-propenyl-

Jaagsiekte

- see Pulmonary Adenomatosis, Ovine

Jaundice, Obstructive

- Kidney Neoplasms
 - Neoplasm Metastasis, 79-5302

Kaempferol

- Guanine, 8-Aza-
 - Mutation, 79-5026
- Mutagenic Activity
 - Hamster V79 Cells, 79-5026

Kanamycin

- Aminoglycosides
 - Ames Test, 79-5012

Karyotyping

- Choriocarcinoma
 - Hydatidiform Mole, 79-5350
- Uterine Neoplasms
 - Hydatidiform Mole, 79-5350

Keratin

- Bladder Neoplasms
 - Retinoic Acid, 79-5395
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Forestomach, Rat, 79-5002

Keratoacanthoma

- Benz(a)anthracene, 7,12-Dimethyl-
 - Neoplasm Regression, Spontaneous, 79-5045
- Burns
 - Cicatrix, Review, 79-4860
- Carcinoma, Epidermoid
 - Precancerous Conditions, 79-5222
- Hypersensitivity, Delayed
 - Neoplasm Regression, Spontaneous, 79-5045
- Immunity, Cellular
 - Neoplasm Regression, Spontaneous, 79-5045
- Precancerous Conditions
 - Diagnosis and Treatment, Review, 79-4862
- Skin Neoplasms
 - Psoriasis, 79-5104
- Virus-Like Particles
 - Ultrastructural Study, 79-5222

Keratoses

- Laryngeal Neoplasms
 - Carcinoma, Epidermoid, 79-5325
 - Histological Study, 79-5325

Kidney Diseases

- Cyclophosphamide
 - Chromosome Aberrations, 79-4994
- Purine-6-thiol
 - Chromosome Aberrations, 79-4994

Kidney Neoplasms

- Acetic Acid, Lead Salt
 - Carcinogenic Potential, Review, 79-4814
- p*-Acetophenetidide
 - Case Report, 79-5006
- Adenocarcinoma
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 79-5083
 - Transplantation, Heterologous, 79-5280
- Cachexia

Kidney Neoplasms (cont'd)

- Animal Model, Mouse, 79-5280
- Immunosuppression, 79-5280
- Carcinoma, Transitional Cell
 - p*-Acetophenetidine, 79-5006
- Jaundice, Obstructive
 - Neoplasm Metastasis, 79-5302
- Lead
 - Carcinogenic Potential, Review, 79-4814
- Neuroblastoma
 - Case Report, 79-5340
 - Neoplasm Metastasis, 79-5340
- Phosphoric Acid, Lead Salt
 - Carcinogenic Potential, Review, 79-4814
- 4,4'-Stilbenediol, α, α' -Diethyl-
 - Case Report, 79-5083
- Virus, Herpes Lucke
 - Perinatal Exposure, 79-5126
 - Seroepidemiology, Review, 79-4873

L Cells

- Lymphocytes
 - Cell Adhesion, 79-5251
- Mammary Neoplasms, Experimental
 - Hybrid Cells, 79-5279

Lactate Dehydrogenase

- Virus, Herpes Simplex 1
 - Immune Serums, 79-5183

Laryngeal Neoplasms

- Carcinoma, Epidermoid
 - Keratoses, 79-5325
 - Leukoplakia, 79-5325
- Diethylamine, *N*-Nitroso-
 - Dose-Response Study, Hamster, 79-4991
- Ethyl Alcohol
 - Epidemiology, Review, 79-4919
- Keratoses
 - Histological Study, 79-5325
- Occupational Hazard
 - Epidemiology, 79-5365
- Polyps
 - Diethylamine, *N*-Nitroso-, 79-4991
- Smoking
 - Animal Model, Hamster, 79-5017
 - Epidemiology, 79-5365
 - Epidemiology, Review, 79-4919
 - Histological Study, 79-5365
 - Precancerous Conditions, 79-5017, 79-5325

Lead

- Ascorbic Acid
 - Metabolism, Review, 79-4844
- Cytochrome P-450
 - Carcinogenic Potential, Review, 79-4814
- Kidney Neoplasms
 - Carcinogenic Potential, Review, 79-4814
- Tobacco
 - Heavy Metal Levels, 79-4944
- Vitamin E
 - Metabolism, Review, 79-4844

Leiomyoma

- Ovarian Neoplasms
 - Epidemiology, 79-5380

Leiomyosarcoma

- Gastrointestinal Neoplasms
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester

Leiomyosarcoma (cont'd)

- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 - 79-4978
- Vulvar Neoplasms
 - Case Report, 79-5351
 - Neoplasm Recurrence, Local, 79-5351

Leucosarcoma

- IgM
 - Immunoglobulins, Surface, 79-5268
- B-Lymphocytes
 - Receptors, Complement, 79-5268
 - Receptors, Fc, 79-5268

Leukemia

- Benzene
 - Occupational Hazard, 79-5358
- Child
 - Epidemiology, Poland, 79-5384
 - Medical History Taking, 79-5384
- Chromosomes
 - Genes, Recessive, Review, 79-4916
- Cyclophosphamide
 - Epidemiology, Review, 79-4817
- Epidemiology
 - Rat, 79-5400
- Ethylene Oxide
 - Carcinogenic Potential, Review, 79-4809
- Genetics
 - Case Report, 79-5289
- Hematological Diseases
 - Precancerous Conditions, 79-5289
- Histocompatibility Antigens
 - Child, 79-5247
 - Parental Compatibility, 79-5247
- Hodgkin's Disease
 - Immunosuppression, Review, 79-4906
- Hyperplasia
 - Lymphoid Tissue, 79-5149
- B-Lymphocytes
 - IgM, 79-4900
- T-Lymphocytes
 - Cell Movement, 79-5251
- Neutrons
 - Carcinogenic Potential, Review, 79-4859
 - Dose-Response Study, Review, 79-4858
- Occupational Hazard
 - Epidemiology, 79-5358
- Radiation, Ionizing
 - Epidemiology, Child, 79-5359
 - Epidemiology, Review, 79-4815
 - Radiography, 79-5385
- Radioactive Fallout
 - Epidemiology, Child, 79-5359
- Virus, Guinea Pig Herpes
 - Lymphoid Tissue, 79-5149
 - Viral Interactions, 79-5149
- Virus, Guinea Pig RNA Tumor
 - Lymphoid Tissue, 79-5149
 - Viral Interactions, 79-5149

Leukemia, Hairy Cell

- Anemia, Aplastic
 - Precancerous Conditions, Review, 79-4901
- B-Lymphocytes
 - Immune Response, Review, 79-4901

Leukemia, Lymphoblastic

- Autoimmune Diseases

Leukemia, Lymphoblastic (cont'd)

- Hyperthyroidism, 79-5267
- Rheumatic Fever, 79-5267

Genetics

- Autoimmune Diseases, 79-5267
- Precancerous Conditions, 79-5289

T-Lymphocytes

- Lymphocyte Depletion, 79-5123
- Mitogens, 79-5123

Virus, Varicella-Zoster

- Pregnancy, 79-5267

Leukemia, Lymphocytic**Complement**

- Lymphocytotoxicity, 79-5237

Concanavalin A

- Binding Sites, Review, 79-4905

Immunologic Deficiency Syndromes

- Case Report, 79-5290
- Histocompatibility Antigens, 79-5290
- B-Lymphocytes, 79-5290

Lymphocytes

- DNA Replication, 79-5250
- Immunologic Capping, Review, 79-4905

T-Lymphocytes

- DNA Replication, 79-5250

Leukemia, Macrocytic

see Anemia, Aplastic

Leukemia, Monocytic

- Benzene
- Occupational Hazard, 79-5358

Leukemia, Myeloblastic

- Alkaline Phosphatase
- Precancerous Conditions, 79-5291

Anemia, Aplastic

- Precancerous Conditions, 79-5291

Bone Marrow

- Precancerous Conditions, 79-5291

DNA

- Transformation, Genetic, 79-5224

Drug Therapy

- Case Report, 79-4995

Eosinophils

- Bone Marrow, 79-5296

Genetics

- Autoimmune Diseases, 79-5267
- Precancerous Conditions, 79-5289

Granulocytes

- Colony Formation, 79-5291
- Precancerous Conditions, 79-5291

Hodgkin's Disease

- Case Report, 79-5103
- Drug Therapy, Combination, 79-5103
- Radiotherapy, 79-5103

Macrophages

- Bone Marrow, 79-5296

Monocytes

- Colony Formation, 79-5291

Radiation, Ionizing

- Adriamycin, 79-4995
- Case Report, 79-4995
- Cyclophosphamide, 79-4995

Virus, RNA Tumor

- Transformation, Genetic, 79-5224

Leukemia, Myelocytic

Anemia

Leukemia, Myelocytic (cont'd)

- Precancerous Conditions, 79-5293

Benz(a)anthracene, 7,12-Dimethyl-
Rat, Germfree, Review, 79-4918

Benzene

- Occupational Hazard, 79-5358

Bone Marrow

- Cell Abnormalities, 79-5293

Chromosomes, Human, 21-22

- Diagnosis, 79-5292

Polycythemia Vera

- Chromosomes, Human, 21-22, 79-5292

Thrombopenia

- Precancerous Conditions, 79-5293

Virus, Herpes Simplex

- Antigen-Antibody Reactions, 79-5191

Leukocytes**Adenocarcinoma**

- Histocompatibility Antigens, 79-5246

Aflatoxin B1

- Chemotaxis, 79-5033

Infectious Mononucleosis

- Virus, Epstein-Barr, 79-5168

Poikiloderma Congenitale

- Immune Response, 79-5269

Virus, Epstein-Barr

- Virus Cultivation, 79-5162

- Virus Replication, 79-5168

Virus, Herpes

- Virus Replication, Review, 79-4877

Virus, Herpes Simplex 2

- Adult, Infant, 79-5195

- Virus Replication, 79-5195

Leukoplakia**Laryngeal Neoplasms**

- Carcinoma, Epidermoid, 79-5325

Leydig Cell Tumor**Testicular Neoplasms**

- Epidemiology, Jamaica, 79-5388
- Gonadotropins, 79-4855

Leydig Cells

- 4,4'-Stilbenediol, α,α' -Diethyl-
Receptors, Hormone, 79-5080

LH

- Benz(a)anthracene, 7,12-Dimethyl-
Serum Levels, 79-5050

Ligands

- Carcinogen, Chemical
- Hepatocarcinogenesis, Review, 79-4841

Light

- Chromosome Aberrations
- Photobiology, Review, 79-4856
- DNA Replication
- Photobiology, Review, 79-4856

Lip Neoplasms

- Smoking
- Epidemiology, Review, 79-4830

Lipids

- Benz(a)anthracene, 7,12-Dimethyl-
Metabolism, Rat, 79-5048
- Carcinoma, Basal Cell
- Cholanthrene, 3-Methyl-, 79-5052
- Dibenz(a,h)anthracene, 79-5052

Lipids (cont'd)

- Carcinoma, Epidermoid
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5052
 - Benzo(a)pyrene, 79-5052
 - Cholanthrene, 3-Methyl-, 79-5052
- Melanoma
 - Growth, 79-5399
- Papilloma
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5052
 - Benzo(a)pyrene, 79-5052
- Sarcoma
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5052
- Skin Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5052
 - Benzo(a)pyrene, 79-5052
 - Cholanthrene, 3-Methyl-, 79-5052
 - Dibenz(a,h)anthracene, 79-5052

Lipopolysaccharides

- Acetic Acid, (Ethylenedinitrilo)tetra-*Escherichia coli*, 79-5092
- Neuroblastoma
 - Lymphocyte Transformation, 79-5255
- Virus, Herpes Simplex 1
 - Immune Response, Mouse, 79-4911
 - Virus Replication, 79-4911

Lipoproteins

- Cell Division
 - Hepatocytes, Review, 79-4938
- Estrogenic Substances, Conjugated
 - Drug Therapy, 79-5354

Liver

- Americium
 - Body Burden, 79-5106
- Benzo(a)pyrene
 - DNA, Binding, 79-5061
- Melanoma
 - Neoplasm Metastasis, 79-5323

Liver Cirrhosis

- Ethyl Alcohol
 - Epidemiology, 79-5356

Liver Diseases

- Androgens
 - Peliosis, Review, 79-4847

Liver Neoplasms

- Acetamide, *N*-Fluoren-2-yl-
 - Fetal Globulins, 79-4907
 - Immune Response, Review, 79-4907
- Adenoma
 - Androgens, 79-4847
 - Contraceptives, Oral, 79-4931, 79-5089
 - Estradiol, 17-Ethynyl-, 79-5086
 - Ethinodiol Diacetate, 79-5086
 - Mestranol, 79-5089
 - Norethisterone Acetate, 79-5086
- Androgens
 - Histological Study, Review, 79-4847
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 - Antigens, Neoplasm, 79-4907
 - Fetal Globulins, 79-4907
 - Immune Response, Review, 79-4907
- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Co-carcinogenic Activity, Review, 79-4836
- Benzo(a)pyrene
 - Hepatectomy, 79-5064

Liver Neoplasms (cont'd)

- Carcinoma
 - Benzene, 4-Allyl-1,2-(methylenedioxy)-, 79-5023
 - Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
- Case Report
 - Contraceptives, Oral, 79-5086
- Cholangioma
 - Thorium Dioxide, 79-5110
- Contraceptives, Oral
 - Epidemiology, Review, 79-4931
- Estrogens
 - Epidemiology, France, 79-5374
- Ethyl Alcohol
 - Co-carcinogenic Activity, Review, 79-4836
- Ethylene, Trichloro-
 - Epidemiology, 79-5375
 - Occupational Hazard, 79-5376
- Hemangioendothelioma
 - Thorium Dioxide, 79-5110
- Hemangioma
 - 12-*O*-Tetradecanoylphorbol-13-acetate, 79-5041
- Mycotoxins
 - Dose-Response Study, Review, 79-4923
 - Mathematical Models, 79-4923
- Neoplasm Metastasis
 - Animal Model, Mouse, 79-5323
- Nitrosamines
 - Structure-Activity Relationship, Review, 79-4828
- Progestational Hormones
 - Epidemiology, France, 79-5374
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Mouse, Nude, 79-5041
- Thorium Dioxide
 - Case Report, 79-5110

LS 1727

- 5 α -Androstan-3-one, 17 β -Hydroxy-
 - Metabolism, 79-5046
- Estradiol
 - Metabolism, 79-5046
- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5046
 - DNA Replication, 79-5046
 - Growth, 79-5046
- Progesterone
 - Metabolism, 79-5046

Lung

- Mammary Neoplasms, Experimental
 - Neoplasm Metastasis, 79-5278, 79-5344

Lung Neoplasms

- Acetic Acid, Mercapto-
 - Macrophages, 79-5257
- Adenocarcinoma
 - Air Pollutants, 79-5019
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
 - Chromium, 79-4946
 - Sex Chromosome, 79-5327
 - Smoking, 79-5368
 - Tuberculosis, Pulmonary, 79-5328
- Adenocarcinoma, Papillary
 - Epidemiology, 79-5370
- Adenoma
 - Air Pollutants, 79-5019
 - Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
 - Methane, Nitro-, 79-5018
 - Urea, Ethyl Nitroso-, 79-4982
- Asbestos

Lung Neoplasms (cont'd)

- Occupational Hazard, 79-5369
- Benzenamine, 4,4'-Methylenebis(2-chloro)-
 - Dietary Proteins, 79-5024
 - Dose-Response Study, Rat, 79-5024
- Carbamic Acid, Ethyl Ester
 - Co-carcinogenic Effect, 79-4982
- Carcinoembryonic Antigen
 - Ascites, Pleural Effusions, 79-5242
- Carcinoma
 - Chromium, 79-4946
 - Colony Stimulating Factor, 79-5326
 - Occupational Hazard, Review, 79-4854
 - Pneumoconiosis, 79-5371
 - Smoking, 79-5371
- Carcinoma, Epidermoid
 - Chromium, 79-4946
 - Epidemiology, 79-5370
 - Smoking, 79-5368
 - Tuberculosis, Pulmonary, 79-5328
- Carcinoma, Oat Cell
 - Epidemiology, 79-5370
 - Smoking, 79-5368
- Chromium
 - Occupational Hazard, 79-4946, 79-5369
 - Precancerous Conditions, 79-4946
- Coal
 - Occupational Hazard, 79-5371
- Colony Stimulating Factor
 - Body Fluids, 79-5326
- Ethnic Groups
 - Epidemiology, Malaysia, 79-5368
- Ethylene, Trichloro-
 - Occupational Hazard, 79-5376
- Fibrosarcoma
 - 1,3-Butadiene, 2-Chloro-, 79-4967
- Gold
 - Pinocytosis, 79-5257
- Granulocytes
 - Colony Stimulating Factor, 79-5326
- Granuloma
 - Neoplasm Metastasis, 79-5278
 - Neoplasm Regression, Spontaneous, 79-5278
- Macrophages
 - Colony Stimulating Factor, 79-5257
 - Pinocytosis, 79-5257
- Mesothelioma
 - Occupational Hazard, Review, 79-4854
- Methane, Nitro-
 - Smoke Condensate, 79-5018
- Neoplasms, Multiple Primary
 - Epidemiology, 79-5355
- Neutrons
 - Carcinogenic Potential, Review, 79-4859
- Occupational Hazard
 - Epidemiology, 79-5364
 - Epidemiology, Norway, 79-5369
- Pneumoconiosis
 - Epidemiology, 79-5371
- Sarcoma
 - Benzo(a)pyrene, 79-5018
- Schizophrenia
 - Epidemiology, 79-5370
- Sex Chromosome
 - Chromosome Aberrations, 79-5327
- Smoking
 - Epidemiology, Malaysia, 79-5368

Lung Neoplasms (cont'd)

- Epidemiology, Review, 79-4830
- Tuberculosis, Pulmonary
 - Smoking, 79-5328
- Uranium
 - Occupational Hazard, 79-5369
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 79-4982
- Virus, Herpes Simplex
 - Antigen-Antibody Reactions, 79-5191

Lupus Erythematosus

- Valine, 3-Mercapto-
 - Neoplasms, 79-4834

Lymphocyte Depletion

- Graft Survival
 - Rat, Nude, 79-5259
- Leukemia, Lymphoblastic
 - T-Lymphocytes, 79-5123
- Virus, Marek's Disease Herpes
 - T-Lymphocytes, 79-5123

Lymphocyte Transformation

- Breast Neoplasms
 - Concanavalin A, 79-5254
 - Plant Agglutinins, 79-5254
- Gastrointestinal Neoplasms
 - Concanavalin A, 79-5254
 - Plant Agglutinins, 79-5254
- Hodgkin's Disease
 - B-Lymphocytes, 79-5294
- Infectious Mononucleosis
 - Immune Serums, 79-5170
 - Plant Agglutinins, 79-5170
- Lymphoma
 - Immunity, Cellular, 79-5159
 - B-Lymphocytes, 79-5294
 - Virus, Varicella-Zoster, 79-5159
- Neuroblastoma
 - Antigens, Neoplasm, 79-5255
 - Concanavalin A, 79-5255
 - Lipopolysaccharides, 79-5255
- Urogenital Neoplasms
 - Neoplasms, Multiple Primary, 79-5281
- Virus, Epstein-Barr
 - Antigens, Viral, 79-5161
 - Fetal Blood, 79-5162
 - B-Lymphocytes, 79-5161
 - Phosphonoacetic Acid, 79-5168
 - Plant Agglutinins, 79-5170
 - Virus Rescue, 79-5162
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 79-5181
 - Plant Agglutinins, 79-5181
 - Tuberculin, 79-5181
- Virus, Varicella-Zoster
 - Antigens, Viral, 79-5159

Lymphocytes

- Aryl Hydrocarbon Hydroxylases
 - Twins, Review, 79-4839
- Burkitt's Lymphoma
 - Immunologic Capping, Review, 79-4905
- Chloramphenicol
 - Chromosome Abnormalities, 79-5043
- Fibroblasts
 - Cell Adhesion, 79-5251
- Hodgkin's Disease

Lymphocytes (cont'd)

- Concanavalin A, 79-4905
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
Chromosome Aberrations, 79-4996
- L Cells
 - Cell Adhesion, 79-5251
- Leukemia, Lymphocytic
 - DNA Replication, 79-5250
 - Immunologic Capping, Review, 79-4905
- Lymphoma
 - Immunologic Capping, Review, 79-4905
- Melanoma
 - Killer Cells, 79-5275
- Nucleotidases
 - Aging, 79-5392
 - Cell Differentiation, 79-5392
- Propane, 1,2-Epoxy-
 - Bone Marrow, 79-4964
 - Chromosome Aberrations, 79-4964
- Radiation, Ionizing
 - Chromatids, 79-5101
- Virus, Herpes Simplex 1
 - Virus Replication, 79-5192
- Virus, Herpes Simplex 2
 - Virus Replication, 79-5192

B-Lymphocytes

- Avian Leukosis
 - Virus, Marek's Disease Herpes, 79-5124
- Carcinoma, Epidermoid
 - Immunologic Deficiency Syndromes, 79-5290
- Heavy Chain Disease
 - Genetics, 79-5252
 - IgA, 79-5252
 - Immunoglobulins, Alpha Chain, 79-5252
- Histocompatibility Antigens
 - Transplantation Immunology, 79-5246
- Hodgkin's Disease
 - Lymphocyte Transformation, 79-5294
- Leucosarcoma
 - Receptors, Complement, 79-5268
 - Receptors, Fc, 79-5268
- Leukemia
 - IgM, 79-4900
- Leukemia, Hairy Cell
 - Immune Response, Review, 79-4901
- Leukemia, Lymphocytic
 - Immunologic Deficiency Syndromes, 79-5290
- Lymphoma
 - Lymphocyte Transformation, 79-5294
- Lymphosarcoma
 - Immunologic Deficiency Syndromes, 79-5290
- Multiple Myeloma
 - Cell Differentiation, Review, 79-4900
 - IgM, 79-4900
- Poikiloderma Congenitale
 - Immune Response, 79-5269
- Radioactive Fallout
 - Chromosome Aberrations, 79-5096, 79-5097
- Sarcoma, Reticulum Cell
 - Case Report, 79-5297
- Virus, Epstein-Barr
 - Antigens, Viral, 79-5171
 - Complement 3, 79-5171
 - Cycloheximide, 79-5161
 - Cytosine, 1- β -D-Arabinofuranosyl-, 79-5161
 - DNA Replication, 79-5161
 - Fetal Blood, 79-5161

B-Lymphocytes (cont'd)

- Killer Cells, Review, 79-4890
- Lymphocyte Transformation, 79-5161
- Lymphocyte Transformation, Review, 79-4890
79-4891, 79-4894
- Virus Replication, Review, 79-4878
- Virus, Herpes
 - Carcinogenic Activity, Review, 79-4883
 - Lymphocyte Transformation, Review, 79-4879
79-4891
- Virus, Herpes Papio
 - Lymphocyte Transformation, Review, 79-4891
- Virus, Herpes Simplex
 - Virus Replication, 79-5174
- Virus, Marek's Disease Herpes
 - Antigens, Viral, 79-5124

T-Lymphocytes

- Antilymphocyte Serum
 - Suppressor Cells, Review, 79-4903
- Cell Movement
 - Lymphocyte Culture Test, Mixed, 79-5251
- Colchicine
 - Cell Migration Inhibition, 79-5251
- Cortisone Acetate
 - Radiation, Ionizing, 79-4903
- Cyclosporin A
 - Lymphocyte Transformation, Review, 79-4904
- Cytochalasin B
 - Cell Migration Inhibition, 79-5251
- Heavy Chain Disease
 - Immunoglobulins, Alpha Chain, 79-5252
- Histocompatibility Antigens
 - Graft vs Host Reaction, 79-5245
 - Graft Rejection, 79-5245
 - Immune Response, Review, 79-4902
 - Immunity, Cellular, 79-5244
 - Killer Cells, 79-5244
 - Lymphocyte Cooperation, Review, 79-4902
- Leukemia
 - Cell Movement, 79-5251
- Leukemia, Lymphoblastic
 - Lymphocyte Depletion, 79-5123
 - Mitogens, 79-5123
- Leukemia, Lymphocytic
 - DNA Replication, 79-5250
- Lymphoma
 - Virus, Marek's Disease Herpes, 79-5124
- Nitrous Acid, Sodium Salt
 - Cell Migration Inhibition, 79-5251
- Papilloma
 - Antilymphocyte Serum, 79-5256
- Pregnancy
 - Transplantation Immunology, 79-5235
- Psoralen, 8-Methoxy-
 - Immunosuppression, 79-5099
- Radiation, Ionizing
 - Suppressor Cells, Review, 79-4903
- Radioactive Fallout
 - Chromosome Aberrations, 79-5096
- Ultraviolet Rays
 - Immunosuppression, 79-5099
- Virus, Herpes
 - Carcinogenic Activity, Review, 79-4883
 - Immunity, Cellular, Review, 79-4874
- Virus, Herpes Simplex
 - Mitogens, 79-5174
 - Virus Replication, 79-5174

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T-Lymphocytes (cont'd)

- Virus, Herpes Simplex 1
 - Immunosuppression, 79-5182
- Virus, Herpes Simplex 2
 - Immunity, Cellular, 79-5194
- Virus, Marek's Disease Herpes
 - Antigens, Viral, 79-5124
 - Immune Response, Review, 79-4890
 - Lymphocyte Depletion, 79-5123
 - Lymphocyte Transformation, Review, 79-4890
 - Mitogens, 79-5123

Lymphoid Tissue

- Hyperplasia
 - Leukemia, 79-5149
- Virus, Guinea Pig Herpes
 - Leukemia, 79-5149
- Virus, Guinea Pig RNA Tumor
 - Leukemia, 79-5149

Lymphokines

- RNA
 - Immunity, Cellular, 79-5234

Lymphoma (General and Unspecified)

- Carcinogen, Chemical
 - Air Pollutants, 79-5019
- Concanavalin A
 - Binding Sites, Review, 79-4905
- Cyclophosphamide
 - Epidemiology, Review, 79-4817
- Dibenz(a,h)acridine
 - Iron Oxide, 79-4947
- Eosinophils
 - Bone Marrow, 79-5296
- Heavy Chain Disease
 - Immunity, Cellular, 79-5252
 - Immunoglobulins, Alpha Chain, 79-5252
- Histocompatibility Antigens
 - Antigen-Antibody Reactions, 79-5270
 - Cell Membrane, 79-5270
- Interferon
 - Immunity, Cellular, 79-5159
- Lymphocyte Transformation
 - Immunity, Cellular, 79-5159
- Lymphocytes
 - Immunologic Capping, Review, 79-4905
- B-Lymphocytes
 - Lymphocyte Transformation, 79-5294
- Macrophages
 - Bone Marrow, 79-5296
- Neoplasms, Multiple Primary
 - Immunohistological Study, 79-5294
- Phosphotransferases
 - Isolation and Characterization, 79-5396
 - Pyrimidine, 79-5396
 - as-Triazine-3,5-(2*H*,4*H*)-dione, 2- β -*D*-Ribofuranosyl-, 79-5396
 - Uracil, 5-Fluoro-, 79-5396
- Radiation, Ionizing
 - Immunogenetics, 79-5270
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 79-4982
- Virus, Epstein-Barr
 - Antigens, Viral, 79-5171
- Virus, Herpes
 - Immune Response, Review, 79-4875
- Virus, Herpes Simplex 1
 - Trigeminal Nerve, 79-5186

Lymphoma (General and Unspecified) (cont'd)

- Virus, Marek's Disease Herpes
 - Histocompatibility Antigens, 79-5121
 - Immunity, Cellular, 79-5122
 - T-Lymphocytes, 79-5124
- Virus, RNA Tumor
 - Carcinogenic Potential, Review, 79-4888
- Virus, Varicella-Zoster
 - Interferon, 79-5159
 - Lymphocyte Transformation, 79-5159

Lymphosarcoma

- Complement
 - Immune Serums, 79-5237
 - Lymphocytotoxicity, 79-5237
- Immunologic Deficiency Syndromes
 - Histocompatibility Antigens, 79-5290
 - B-Lymphocytes, 79-5290
- Stomach Neoplasms
 - Epidemiology, 79-5377
- Testicular Neoplasms
 - Epidemiology, Jamaica, 79-5388
- Transplantation Immunology
 - Mouse, Nude, 79-5271

Lysosomes

- Virus, Polyoma
 - DNA, Viral, 79-5206
 - Viral Proteins, 79-5206

Macrophages

- Graft vs Host Reaction
 - Bone Marrow, 79-5296
 - Hematological Diseases
 - Bone Marrow, 79-5296
 - Histocompatibility Antigens
 - Transplantation Immunology, 79-5246
 - Leukemia, Myeloblastic
 - Bone Marrow, 79-5296
 - Lung Neoplasms
 - Acetic Acid, Mercapto-, 79-5257
 - Colony Stimulating Factor, 79-5257
 - Pinoeytosis, 79-5257
 - Methionine, *S*-Adenosyl-
 - Methyltransferases, 79-5258
 - Phosphatidylethanolamines
 - Methyltransferases, 79-5258
 - Phospholipids
 - Chemotactic Factors, 79-5258
 - Methylation, 79-5258
 - RNA
 - Cell Migration Inhibition, 79-5234
 - Smoking
 - Glutathione Peroxidase, 79-5015
 - Phagocytosis, 79-5015
 - Superoxide Dismutase, 79-5015
 - Virus, Herpes Simplex 1
 - Cell Migration Inhibition, 79-5181
 - Immunity, Cellular, 79-5181
 - Immunosuppression, 79-5182
 - Virus, Herpes Simplex 2
 - Immunity, Cellular, 79-5194
- ### Magnesium
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Mineralization, Kidney, 79-5082
 - Virus, Moloney Murine Leukemia
 - DNA Replication, 79-5132

- Malaria**
Virus, Epstein-Barr
Immunity, Cellular, Review, 79-4882
- Malathion**
Chromatids
Chromosome Aberrations, 79-4971
Fibroblasts, 79-4971
- Mammæ**
Benz(a)anthracene, 7,12-Dimethyl-
Body Burden, Rat, 79-5048
- Mammary Neoplasms, Experimental**
Adenocarcinoma
Benz(a)anthracene, 7,12-Dimethyl-, 79-4918
Benzenamine, 4,4'-Methylenebis(2-chloro)-, 79-5024
Ethane, 1,2-Dichloro-, 79-4961
Adenofibroma
Epidemiology, Rat, 79-5400
Adenoma
Diet, 79-5397
Antigens, Neoplasm
Hybrid Cells, 79-5279
Benz(a)anthracene, 7,12-Dimethyl-
Histological Study, Rat, 79-5049
Hydroxylamine, 79-5049
LS 1727, 79-5046
Norgestrel, 79-5046
Rat, Germfree, Review, 79-4918
Receptors, Hormone, 79-5047
Urea, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitroso-
79-5046
Ethane, 1,2-Dichloro-
Carcinogenic Activity, Mouse, Rat, 79-4961
Ethylene, Chloro-
Carcinogenic Activity, Review, 79-4808
Histocompatibility Antigens
Hybrid Cells, 79-5279
Hyperplasia
Hydroxylamine, 79-5049
L Cells
Hybrid Cells, 79-5279
LS 1727
DNA Replication, 79-5046
Lung
Neoplasm Metastasis, 79-5278, 79-5344
Neoplasm Circulating Cells
Immune Response, Mouse, 79-5278
Norgestrel, Nitrosocarbamate
Growth, 79-5046
Prolactin
DNA Replication, 79-5047
Receptors, Hormone, 79-5047
Virus, Murine Mammary Tumor
Neoplasm Metastasis, 79-5344
- Mammography**
Adipose Tissue
Radiation Effects, 79-4863
Risk Factors
Dose-Response Study, Review, 79-4863
- Manganese**
Tobacco
Heavy Metal Levels, 79-4944
Virus, Moloney Murine Leukemia
DNA Replication, 79-5132
- Manganese Dioxide**
Respiratory Tract Neoplasms
Benzo(a)pyrene, 79-4947
- α,β -Mannitone**
Gasoline Substitute
Carcinogenic Potential and Toxicity, Review
79-4831
Papilloma
Carcinogenic Potential and Toxicity, Review
79-4831
- Marihuana**
see Cannabis
- Megakaryocytes**
Anemia, Aplastic
Bone Marrow, 79-5288
- Melanin**
Melanoma
Cycloheximide, 79-5231
Puromycin, 79-5231
Neoplasms, Experimental
Drosophila melanogaster, 79-5282
- Melanoma**
Antibody Specificity
Hybrid Cells, 79-5263
Antigens, Neoplasm
Antibody Specificity, 79-5263
Cell Membrane, 79-5276
Isolation and Characterization, 79-5276
Beta 2 Microglobulin
Antigenic Determinants, 79-5276
Cholesterol
Metabolism, 79-5399
Cycloheximide
Melanin, 79-5231
Cytotoxins
Antigen-Antibody Complex, 79-5239
Eye Neoplasms
Epidemiology, Review, 79-4922
Fibrinolysis
Neoplasm Metastasis, 79-5307
Gangliosides
Metabolism, 79-5399
Genetics
Killer Cells, 79-5275
RH-HR Blood-Group System, 79-5275
Histocompatibility Antigens
Antigenic Determinants, 79-5276
Hypercalcemia
Case Report, 79-5324
Neoplasm Metastasis, 79-5324
Hyperparathyroidism
Neoplasm Metastasis, 79-5324
Parathyroid Hormone, 79-5324
IgG
Antigen-Antibody Complex, 79-5239
Lipids
Growth, 79-5399
Liver
Neoplasm Metastasis, 79-5323
Lymphocytes
Killer Cells, 79-5275
Neoplasm Metastasis
Animal Model, Mouse, 79-5323
Bones, 79-5324
Phospholipids

Melanoma (cont'd)

- Metabolism, 79-5399
- Plasmacytoma
 - Hybrid Cells, 79-5263
- Precancerous Conditions
 - Diagnosis and Treatment, Review, 79-4862
- Puromycin
 - Melanin, 79-5231
- Smoking
 - Immune Response, 79-5016
 - Neoplasm Metastasis, 79-5016
- Uridine, 2'-Deoxy-5-iodo-
 - Virus Activation, 79-5231
- Virus, Hamster C-Type RNA Tumor
 - Isolation and Characterization, 79-5148
- Virus, Murine Leukemia
 - Virus Activation, 79-5231
- Virus, Murine Sarcoma
 - Virus Cultivation, 79-5231

Membrane Proteins

- Virus, Mink Cell Focus-Inducing
 - Antigenic Determinants, 79-5145
- Virus, Murine Leukemia
 - Antigenic Determinants, 79-5145
- Virus, Sendai
 - Triton X 100, 79-5229
- Virus, SV40
 - Cell Transformation, Neoplastic, 79-5218

Meningioma

- Brain Neoplasms
 - Case Report, Psychiatric Symptoms, 79-5310
- Nervous System Neoplasms
 - Ultrastructural Study, 79-5316

Menkes Syndrome

- see Brain Diseases, Metabolic

Mercury, Methyl-

- Environmental Hazard
 - Epidemiology, Review, 79-4811

Mesothelioma

- Asbestos
 - Epidemiology, Review, 79-4815
- Lung Neoplasms
 - Occupational Hazard, Review, 79-4854
- Respiratory Tract Neoplasms
 - Asbestos, 79-4978

Mestranol

- Liver Neoplasms
 - Adenoma, 79-5089

Metaplasia

- Intestinal Neoplasms
 - Carrageen, 79-5036
- Stomach Neoplasms
 - Precancerous Conditions, 79-5378

Methane, Azoxy-

- Colonic Neoplasms
 - Adenocarcinoma, 79-4955
 - Pancreaticobiliary Diversion, 79-4955
- Intestinal Neoplasms
 - Adenocarcinoma, Papillary, 79-4955
 - Carcinoma, Mucinous, 79-4955
 - Pancreaticobiliary Diversion, 79-4955

Methane, Nitro-

- Lung Neoplasms

Methane, Nitro- (cont'd)

- Adenoma, 79-5018
- Smoke Condensate, 79-5018
- Thyroid Gland
 - Organ Weight, 79-4976
- Thyroxine
 - Serum Levels, 79-4976

Methanesulfonic Acid, Ethyl Ester

- Ames Test
 - Dose-Response Study, 79-5059
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Co-mutagenic Activity, 79-5059
- Saccharomyces cerevisiae*
 - DNA Repair, 79-4953

Methanesulfonic Acid, Methyl Ester

- Chromatids
 - Fish, 79-4998
- Chromosome Aberrations
 - Micronucleus Test, 79-4996
- Erythroleukemia
 - Virus, Friend Murine Leukemia, 79-4952
- Mutagenic Activity
 - Mammals, Microorganisms, Review, 79-4835
- Saccharomyces cerevisiae*
 - DNA Repair, 79-4953
- Virus, Friend Murine Leukemia
 - Antibody Formation, 79-4952
 - Co-carcinogenic Effect, 79-4952

Methionine

- Polycyclic Hydrocarbons
 - Amino Acyl T RNA Synthetases, 79-5069
 - RNA, Transfer, 79-5069

Methionine, S-Adenosyl-

- Macrophages
 - Methyltransferases, 79-5258

Methyltransferases

- Macrophages
 - Methionine, S-Adenosyl-, 79-5258
 - Phosphatidylethanolamines, 79-5258

Metronidazole

- see Imidazole-1-ethanol, 2-Methyl-5-nitro-

Mevinphos

- see Crotonic Acid, 3-Hydroxy-, Methyl Ester, Dimethyl Phosphate

Microsomes

- Benzo(a)pyrene
 - DNA, Binding, 79-5085
- Estradiol
 - DNA, Binding, 79-5085

Microsomes, Liver

- Ammonium Sulfate
 - Mixed Function Oxidases, 79-4989
 - NADPH Cytochrome C Reductase, 79-4989
- Benzo(a)pyren-9-ol 4,5-Oxide
 - DNA Adducts, 79-5062
- Benzo(a)pyrene
 - DNA Adducts, 79-5062
 - DNA, Binding, 79-5061
- Benzo(a)pyrene, 6-Acetoxyethyl-
 - DNA, Binding, 79-5065
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - DNA Adducts, 79-5062

- Microsomes, Liver (cont'd)**
 Benzo(a)pyrene-6-methanol
 Cholanthrene, 3-Methyl-, 79-5065
 Benzo(a)pyrene 4,5-Oxide
 DNA Adducts, 79-5062
 Benzo(e)pyrene
 Ames Test, 79-5060
 Benzo(e)pyrene, 9,10-Dihydro-
 Ames Test, 79-5060
 Benzo(e)pyrene, 4,4-Dihydro-4,5-dihydroxy-
 Ames Test, 79-5060
 Benzo(e)pyrene, 9,10-Dihydro-9,10-dihydroxy-
 Ames Test, 79-5060
 Cycloheptylamine
 Deamination Products, 79-4970
 Cycloheximide
 Adenosine Triphosphatase, 79-4969
 Glucosphosphatase, 79-4969
 Mixed Function Oxidases, 79-4969
 Cyclohexylamine
 Deamination Products, 79-4970
 Cyclopentylamine
 Deamination Products, 79-4970
 Dieldrin
 Metabolism, 79-5068
 Dimethylamine, *N*-Nitroso-
 Metabolism, 79-4989
 Ethyl Alcohol
 Aryl Hydrocarbon Hydroxylases, 79-4956
 Cytochrome P-450, 79-4956
 Propane, 1,2-Epoxy-3,3,3-trichloro-
 Aminopyrine *N*-Demethylase, 79-4965
 Aryl Hydrocarbon Hydroxylases, 79-4965
- Milk Proteins**
 Immunologic Deficiency Syndromes
 Antigen-Antibody Complex, 79-5240
- Millardia *meltada***
 Virus, C-Type RNA Tumor
 Virus Activation, 79-5140
 Virus, Kirsten Murine Leukemia
 Cell Transformation, Neoplastic, 79-5140
 Virus, Murine Sarcoma
 Cell Transformation, Neoplastic, 79-5140
- Mitogens**
 Leukemia, Lymphoblastic
 T-Lymphocytes, 79-5123
 Virus, Herpes Simplex
 T-Lymphocytes, 79-5174
 Virus, Herpes Simplex 1
 Cell Supernatant, 79-5187
 DNA Replication, 79-5187
 Virus, Herpes Simplex 2
 Cell Supernatant, 79-5187
 DNA Replication, 79-5187
 Virus, Marek's Disease Herpes
 T-Lymphocytes, 79-5123
- Mitomycin C**
 Virus, SV40
 Virus Replication, 79-5209
- Mixed Function Oxidases**
 Ammonium Sulfate
 Microsomes, Liver, 79-4989
 Aniline, *N,N*-Dimethyl-
 Ammonium Sulfate, 79-4989
 Cycloheximide
- Mixed Function Oxidases (cont'd)**
 Microsomes, Liver, 79-4969
 Dimethylamine, *N*-Nitroso-
 Ammonium Sulfate, 79-4989
 1-Naphthalenesulfonic Acid, 8-(Phenylamino)-
 Ammonium Sulfate, 79-4989
- Monocytes**
 Fibrosarcoma
 Cell Aggregation, 79-5285
 Leukemia, Myeloblastic
 Colony Formation, 79-5291
- Monuron**
 see Urea, 3-(*p*-Chlorophenyl)-1,1-dimethyl-
- Mouth Neoplasms**
 Ethylene, Trichloro-
 Occupational Hazard, 79-5376
- Multiple Myeloma**
 Eosinophils
 Bone Marrow, 79-5296
 B-Lymphocytes
 Cell Differentiation, Review, 79-4900
 IgM, 79-4900
 Macrophages
 Bone Marrow, 79-5296
- Multiple Sclerosis**
 Virus, Herpes Simplex 1
 Trigeminal Nerve, 79-5186
- Mutagens**
 Ames Test
 Ampicillin Resistance, Review, 79-4804
 S9 Fraction, Review, 79-4804
 Chromatids
 Fetus, Mouse, 79-4941
 Chromosome Aberrations
 Erythrocytes, 79-4908
 Genetics, Review, 79-4835
 Micronucleus Test, 79-4908
 Screening Tests, Review, 79-4801
 DNA Repair
 Screening Tests, Review, 79-4801
Fusarium moniliforme
 Ames Test, 79-5028
 Isolation and Characterization, 79-5028
- Mutation**
 Dimethylamine, *N*-Nitroso-
Salmonella typhimurium, 79-4988
 DNA Repair
Saccharomyces cerevisiae, 79-4953
 Ethylene, Chloro-
 Guanine, 8-Aza-, 79-4959
 Oubain, 79-4959
 Flavone, 3,3',4',5,7-Pentahydroxy-
 Guanine, 8-Aza-, 79-5026
 Kaempferol
 Guanine, 8-Aza-, 79-5026
 Myeloma Proteins
 DNA Sequence, 79-5238
 Radiation, Ionizing
 Genetic Effects, Review, 79-4865
 Genetic Risks, 79-5385
 Ultraviolet Rays
Saccharomyces cerevisiae, 79-4953

Mycotoxins

- Ammonia
 - Hepatotoxicity, 79-5031
- Environmental Hazard
 - Epidemiology, Review, 79-4811
- Food Contamination
 - Hepatotoxicity, 79-5031
- Liver Neoplasms
 - Dose-Response Study, Review, 79-4923
 - Mathematical Models, 79-4923
- Mutagenic Activity
 - Mammals, Microorganisms, Review, 79-4835

Myeloma Proteins

- Amino Acids
 - Galactin-Binding Proteins, 79-5238
- Immunoglobulins, Heavy Chain
 - Amino Acids, 79-5238
- Mutation
 - DNA Sequence, 79-5238
- Plasmacytoma
 - Clone Cells, 79-5264

Myoblastoma

- Bile Duct Neoplasms
 - Blacks, 79-5329
 - Case Report, 79-5329
 - Cholecystitis, 79-5329
- Esophageal Neoplasms
 - Case Report, 79-5332

Myosarcoma

- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
- Asbestos, 79-4978

Myxomatosis, Infectious

- Virus, Pox
 - Animal Pest Control, Review, 79-4897

Myxosarcoma

- 12-*O*-Tetradecanoylphorbol-13-acetate
- Mouse, Nude, 79-5041

NADP

- Cyclohexylamine
- Metabolism, 79-4970

NADPH Cytochrome C Reductase

- Ammonium Sulfate
- Microsomes, Liver, 79-4989

Naphthalene

- Diol Epoxides
- Electronic Structures, 79-5037

1-Naphthalenesulfonic Acid, 8-(Phenylamino)-

- Ammonium Sulfate
- Mixed Function Oxidases, 79-4989

1-Naphthylamine

- Arylnitrenium Ions
- Mutagenic Activity, 79-5038

2-Naphthylamine

- Arylnitrenium Ions
- Mutagenic Activity, 79-5038
- Bladder Neoplasms
 - Carcinoma, 79-4864
- Pancreatic Neoplasms
 - Occupational Hazard, 79-5373

Nasopharyngeal Neoplasms

- Carcinoma, Epidermoid

Nasopharyngeal Neoplasms (cont'd)

- Diagnosis, 79-5322
- Sarcoma, Reticulum Cell
 - Diagnosis, 79-5322
- Virus, Epstein-Barr
 - Antibodies, Viral, 79-5166, 79-5167
 - Carcinogenic Potential, Review, 79-4888
 - Epidemiology, Review, 79-4894
 - IgA, 79-5166
 - Molecular Biology, Review, 79-4896
 - Saliva, 79-5166
 - Seroepidemiology, Review, 79-4873

Necrosis

- Carcinoma, Basal Cell
 - Graft Rejection, 79-5271

Neoplasm Circulating Cells

- Mammary Neoplasms, Experimental
 - Immune Response, Mouse, 79-5278

Neoplasm Metastasis

- Adenocarcinoma
 - Fibrinolysis, 79-5307
 - Virus, Herpes Simplex 1, 79-5184
- Bladder Neoplasms
 - Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-79-4993
- Brain Neoplasms
 - Adenoma, 79-5298
 - Wounds and Injuries, 79-5109
- Carcinoma
 - Virus, Shope Rabbit Papilloma, 79-5150
- Choriocarcinoma
 - Hydatidiform Mole, 79-5350
- Cicatrix
 - Capillaries, 79-5287
- Clostridiopeptidase A
 - Basement Membrane, 79-5317
- Colonization Potential
 - Animal Model, Mouse, 79-5344
- Digestive System Neoplasms
 - Carcinoembryonic Antigen, 79-5331
- Eye Neoplasms
 - Surgery, Operative, Review, 79-4922
- Head and Neck Neoplasms
 - Carcinoma, Epidermoid, 79-5311
- Hepatoma
 - Brain, 79-5109
 - Wounds and Injuries, 79-5109
- Intestinal Neoplasms
 - Carcinoid Tumor, 79-5337
- Kidney Neoplasms
 - Jaundice, Obstructive, 79-5302
 - Neuroblastoma, 79-5340
- Liver Neoplasms
 - Animal Model, Mouse, 79-5323
- Lung Neoplasms
 - Granuloma, 79-5278
- Mammary Neoplasms, Experimental
 - Lung, 79-5278, 79-5344
 - Virus, Murine Mammary Tumor, 79-5344
- Melanoma
 - Animal Model, Mouse, 79-5323
 - Bones, 79-5324
 - Fibrinolysis, 79-5307
 - Hypercalcemia, 79-5324
 - Hyperparathyroidism, 79-5324
 - Liver, 79-5323

Neoplasm Metastasis (cont'd)

- Smoking, 79-5016
- Ovarian Neoplasms
 - Epidemiology, 79-5380
- Pancreatic Neoplasms
 - Adenocarcinoma, 79-5302
 - Case Report, 79-5302
- Pituitary Neoplasms
 - Adenoma, 79-5298
- Skin Neoplasms
 - Carcinoma, Epidermoid, 79-5390
- Testicular Neoplasms
 - Histocompatibility Antigens, 79-5249
- Virus, Herpes Simplex 1
 - Histocompatibility Antigens, 79-5184
 - Immunization, 79-5184
- Virus, Shope Rabbit Papilloma
 - DNA, Viral, 79-5150

Neoplasm Recurrence, Local

- Nephroblastoma
 - Case Report, 79-5340
- Vulvar Neoplasms
 - Leiomyosarcoma, 79-5351

Neoplasm Regression, Spontaneous

- Keratoacanthoma
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5045
 - Hypersensitivity, Delayed, 79-5045
 - Immunity, Cellular, 79-5045
- Lung Neoplasms
 - Granuloma, 79-5278

Neoplasm Transplantation

- Fibrosarcoma
 - Virus, Herpes Simplex 2, 79-5236
- Intestinal Neoplasms
 - Adenocarcinoma, 79-5035
 - Ileal Tumor, 79-5035
- Sarcoma
 - Histocompatibility Antigens, 79-5248
- Sarcoma, Mast Cell
 - Antigen-Antibody Reactions, 79-5273
- Virus, Herpes Simplex 2
 - Immunosuppression, 79-5236
 - Radiation, Ionizing, 79-5236

Neoplasms (General and Unspecified)

- p*-Benzoquinone, 2,3,5-Tris(1-aziridinyl)-
 - Drug Therapy, Review, 79-4834
- Blood Pressure
 - Epidemiology, 79-5386
- Chromosomes
 - Genes, Recessive, Review, 79-4916
- Gene, Yellow
 - Mouse, Nude, 79-5260
- Gonadotropins, Chorionic
 - Endocrine Abnormalities, Review, 79-4850
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - DNA Repair, 79-5200
- Latency Period
 - Epidemiology, 79-5353
- Lupus Erythematosus
 - Valine, 3-Mercapto-, 79-4834
- Mathematical Model
 - Epidemiology, 79-5353
- Stress, Psychological
 - Immune Response, Review, 79-4934
- Virus, Adeno 5

Neoplasms (General and Unspecified) (cont'd)

- Virus Activation, 79-5200

Neoplasms, Experimental

- Acetic Acid, (2,4,5-Trichlorophenoxy)-
 - Dose-Response Study, Mouse, Review, 79-4832
- Adenosine Cyclic 3',5' Monophosphate
 - Growth, Review, 79-4937
- Aryl Hydrocarbon Hydroxylases
 - Genetics, Mouse, Review, 79-4840
- Autoantibodies
 - Complement Fixation Tests, 79-5274
 - IgM, 79-5274
 - Transplantation Immunology, 79-5274
- Carcinogen, Chemical
 - Risk Evaluation, Review, 79-4806
- Cholanthrene, 3-Methyl-
 - Antigen-Antibody Reactions, 79-5054
 - Immunization, 79-5054
 - Transplantation Immunology, 79-5235
- Virus, Herpes Simplex 2, 79-5196

Drosophila melanogaster

- Adipose Tissue, 79-5282
- Melanin, 79-5282

Fibroblasts

- Transplantation, Homologous, 79-5285

Glycoproteins

- Hybrid Cells, 79-5261
- Mouse, Nude, 79-5261

Guanosine Cyclic 3',5' Monophosphate

- Growth, Review, 79-4937

Hemocytes

- Cell Aggregation, 79-5282
- Phagocytosis, 79-5282

Immunity, Cellular

- Gene, Yellow, 79-5260

Panfurin-S

- Dose-Response Study, Mouse, 79-5011

Pregnancy

- Transplantation Immunology, 79-5235

Transplantation Immunology

- Suppressor Cells, Review, 79-4903

Neoplasms, Multiple Primary

- Adenocarcinoma
 - Case Report, 79-5348
- Breast Neoplasms
 - Epidemiology, 79-5355
- Carcinoma, Transitional Cell
 - Case Report, 79-5348
- Cylindroma
 - Ultrastructural Study, 79-5321
- Digestive System Neoplasms
 - Adenocarcinoma, 79-5348
 - Epidemiology, 79-5355
- Head and Neck Neoplasms
 - Epidemiology, 79-5355
 - Ethyl Alcohol, 79-5355
 - Smoking, 79-5355
- Hodgkin's Disease
 - Immunohistological Study, 79-5294
 - Immunosuppression, Review, 79-4906
- Intestinal Neoplasms
 - Carcinoid Tumor, 79-5337
- Lung Neoplasms
 - Epidemiology, 79-5355
- Lymphoma
 - Immunohistological Study, 79-5294

Neoplasms, Multiple Primary (cont'd)

- Prostatic Neoplasms
 - Epidemiology, 79-5355
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 79-5083
- Psoriasis
 - Case Report, 79-5104
- Skin Neoplasms
 - Ultrastructural Study, 79-5321
- Spinal Cord Neoplasms
 - Neurilemmoma, 79-5314
- Sweat Gland Neoplasms
 - Ultrastructural Study, 79-5321
- Urogenital Neoplasms
 - Adenocarcinoma, 79-5348
 - Carcinoma, Transitional Cell, 79-5348
 - Hypersensitivity, Delayed, 79-5281
 - Immune Response, 79-5281
 - Lymphocyte Transformation, 79-5281

Neoplastic Endocrine-Like Syndromes

- Apudoma
 - Classification, Review, 79-4912

Nephroblastoma

- Child
 - Epidemiology, Review, 79-4925
- Neoplasm Recurrence, Local
 - Case Report, 79-5340

Nervous System

- Quinoline, 4-(Hydroxyamino)-, 1-Oxide
 - Tissue Distribution, 79-5007
- Quinoline, 4-Nitro-, 1-Oxide
 - Tissue Distribution, 79-5007
- Virus, Herpes Simplex 1
 - Virus Replication, 79-5192
- Virus, Herpes Simplex 2
 - Virus Replication, 79-5192

Nervous System Neoplasms

- Fibroma
 - Ultrastructural Study, 79-5316
- Meningioma
 - Ultrastructural Study, 79-5316

Neuraminidase

- Virus, Sendai
 - Glycoproteins, 79-5229

Neurilemmoma

- DNA
 - Cell Division, 79-5224
- Spinal Cord Neoplasms
 - Case Report, 79-5314
- Neoplasms, Multiple Primary, 79-5314

Neuroblastoma

- Adenine
 - Metabolism, 79-5393
- Adenosine
 - Metabolism, 79-5393
- Adrenal Gland Neoplasms
 - Cell Line, 79-5304
 - Ultrastructural Study, 79-5304
- Antigens, Neoplasm
 - Lymphocyte Transformation, 79-5255
- Cell Membrane
 - Isolation and Characterization, 79-5394
- Cells, Cultured
 - Isolation and Characterization, 79-5394
- Child

Neuroblastoma (cont'd)

- Epidemiology, Review, 79-4925
- Coformycin
 - Metabolism, 79-5393
- Concanavalin A
 - Lymphocyte Transformation, 79-5255
- Homocysteine, S-Adenosyl-
 - Adenine, 79-5393
- Homocysteine, S-Tubercidinyl-
 - Metabolism, 79-5393
- Immunity, Cellular
 - Lymphocyte Culture Test, Mixed, 79-5255
- Kidney Neoplasms
 - Case Report, 79-5340
 - Neoplasm Metastasis, 79-5340
- Lipopolysaccharides
 - Lymphocyte Transformation, 79-5255
- Transplantation, Heterologous
 - Mouse, Nude, 79-5304
- Virus, Herpes Simplex 1
 - Virus Replication, 79-5241
- Virus, Herpes Simplex 2
 - Virus Replication, 79-5241
- Virus, Vesicular Stomatitis
 - Cell Fusion, 79-5232

Neurons

- Virus, Herpes Simplex
 - Virus Replication, Review, 79-4878

Neutral Red

- Chromatids
 - Fish, 79-4998

Neutrons

- Leukemia
 - Carcinogenic Potential, Review, 79-4859
 - Dose-Response Study, Review, 79-4858
- Lung Neoplasms
 - Carcinogenic Potential, Review, 79-4859

Neutrophils

- Fibrosarcoma
 - Cell Aggregation, 79-5285

Nickel

- Carcinogen, Chemical
 - Occupational Hazard, Review, 79-4813
- Nose Neoplasms
 - Carcinoma, 79-4948
 - Occupational Hazard, 79-4948
 - Precancerous Conditions, 79-4948

Nicotine

- Smoking
 - Epidemiology, Review, 79-4830
 - Precancerous Conditions, Review, 79-4845

Nicotine, 1'-Demethyl-1'-nitroso-

- Salivary Gland Neoplasms
 - Carcinoma, 79-5013
 - Ultrastructural Study, Mouse, 79-5013

Nitrazepam

- see 2*H*-1,4-Benzodiazepin-2-one, 1,3-Dihydro-7-nitro-5-phenyl-

Nitrogen Monoxide

- Chromosome Aberrations
 - Bone Marrow, 79-4960
 - Spermatozoa, 79-4960
- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-

Nitrogen Monoxide (cont'd)

- Carcinogenic, Teratogenic Potential, Rat, 79-4960
- Chromosome Aberrations, 79-4960

Nitrosamines

- Dialkyl Derivatives
 - Fragmentation, Review, 79-4826
- Environmental Hazard
 - Carcinogenic Potential, Review, 79-4836
- Esophageal Neoplasms
 - Structure-Activity Relationship, Review, 79-4828
- Ethyl Alcohol
 - Fragmentation Products, Review, 79-4823
- Food Contamination
 - Animal Diet, Review, 79-4825
- β -Hydroxy Derivatives
 - Fragmentation Products, Review, 79-4823
- Liver Neoplasms
 - Structure-Activity Relationship, Review, 79-4828
- Nitrous Acid
 - Dealkylation Reactions, Review, 79-4826
- Pesticides
 - Environmental Pollution, Review, 79-4827
- Pyrrolidine, 1-Nitroso-
 - Food Contamination, 79-4828
- Structure-Activity Relationship
 - Carcinogenic Metabolite, Review, 79-4822, 79-4920
 - Dialkyl and Aralkyl Derivatives, Review, 79-4820
 - Electronic Delocalization, 79-4987
 - Stereochemical Effects, Review, 79-4821

Nitroso Compounds

- p*-Acetophenetidine, *N*-Hydroxy-
 - Metabolism, Review, 79-4818
- p*-Acetophenetidine
 - Metabolism, Review, 79-4818
- Carcinogen, Chemical
 - Isolation and Characterization, Review, 79-4927
- Food Contamination
 - Review, 79-4824
- Hydantoin, 1-((5-Nitrofurfurylidene)amino)-
 - Drug Contamination, 79-5010
- Imipramine Hydrochloride
 - Drug Contamination, 79-5010
- Nuclear Magnetic Resonance
 - Internal Rotation, 79-5003
 - p*-Substituted Derivatives, 79-5003
- Phenethylhydrazine Sulfate
 - Drug Contamination, 79-5010

Nitrous Acid

- Nitrosamines
 - Dealkylation Reactions, Review, 79-4826

Nitrous Acid, Sodium Salt

- Clostridium botulinum*
 - Spore Germination, 79-4975
- Food Additives
 - Risk Factors, Review, 79-4819
- T-Lymphocytes
 - Cell Migration Inhibition, 79-5251
- Salmonella typhimurium*
 - Metabolism, 79-4974

Norethisterone Acetate

- Liver Neoplasms
 - Adenoma, 79-5086

Norgestrel

- Mammary Neoplasms, Experimental

Norgestrel (cont'd)

- Benz(a)anthracene, 7,12-Dimethyl-, 79-5046

Norleucine, 6-Diazo-5-oxo-

- DNA Repair
 - N*-Diazoacetyl Derivatives, 79-4999
- Serine, Diazoacetate (Ester)
 - Alkylation, 79-4999

Nose Neoplasms

- Carcinoma
 - Nickel, 79-4948
- Nickel
 - Occupational Hazard, 79-4948
 - Precancerous Conditions, 79-4948
- Occupational Hazard
 - Epidemiology, 79-4948

Nucleic Acids

- Diethylamine, *N*-Nitroso-
 - Alkylation, 79-4990
- Barbituric Acid, 5-Ethyl-5-phenyl-, 79-4990
- Cholanthrene, 3-Methyl-, 79-4990
- Liver, Mouse, 79-4990
- 4-Pantoic Acid, 2-(Diethylamino)ethyl-2-phenyl-2-(2-propene)-, 79-4990
- Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester, HCl, 79-4990
- Virus, Herpes Simplex 1
 - Virus Replication, Review, 79-4885
- Virus, Herpes Simplex 2
 - Virus Replication, Review, 79-4885

Nucleoproteins

- Virus, C-Type RNA Tumor
 - DNA, 79-5225

Nucleotidases

- Aging
 - Lymphocytes, 79-5392
- Nucleotides, 79-5392
- Cell Differentiation
 - Lymphocytes, 79-5392

Nucleotide Sequence

- Virus, Adeno 3
 - RNA, Messenger, 79-5202
- Virus, Adeno 7
 - RNA, Messenger, 79-5202

Nucleotides

- Cell Division
 - Hepatocytes, Review, 79-4938
- Nucleotidases
 - Aging, 79-5392
- Virus, Moloney Murine Leukemia
 - DNA Replication, 79-5132

Obesity

- Uterine Neoplasms
 - Carcinoma, 79-5383
 - Epidemiology, Review, 79-4933

Occupational Hazard

- Asbestosis
 - Epidemiology, Germany, 79-4854
- Bladder Neoplasms
 - Ethylene, Trichloro-, 79-5376
- Bronchitis
 - Chromium, 79-4946
- Carcinogen, Chemical
 - Identification, Review, 79-4920

Occupational Hazard (cont'd)

- Digestive System Neoplasms
 - Epidemiology, 79-5361
 - Ethylene Oxide
 - Epidemiology, Review, 79-4809
 - Ethylene, Trichloro-
 - Epidemiology, 79-5376
 - 2-Imidazolidinethione
 - Epidemiology, Review, 79-4833
 - Laryngeal Neoplasms
 - Epidemiology, 79-5365
 - Leukemia
 - Benzene, 79-5358
 - Epidemiology, 79-5358
 - Leukemia, Monocytic
 - Benzene, 79-5358
 - Leukemia, Myelocytic
 - Benzene, 79-5358
 - Liver Neoplasms
 - Ethylene, Trichloro-, 79-5376
 - Lung Neoplasms
 - Asbestos, 79-5369
 - Chromium, 79-4946, 79-5369
 - Coal, 79-5371
 - Epidemiology, 79-5364
 - Epidemiology, Norway, 79-5369
 - Ethylene, Trichloro-, 79-5376
 - Uranium, 79-5369
 - Mouth Neoplasms
 - Ethylene, Trichloro-, 79-5376
 - Nose Neoplasms
 - Epidemiology, 79-4948
 - Nickel, 79-4948
 - Pancreatic Neoplasms
 - Benzidine, 79-5373
 - Epidemiology, France, 79-5373
 - 2-Naphthylamine, 79-5373
 - Pneumoconiosis
 - Epidemiology, 79-5364
 - Pulmonary Emphysema
 - Chromium, 79-4946
 - Pulmonary Fibrosis
 - Chromium, 79-4946
 - Radiation, Ionizing
 - Genetic Effects, Review, 79-4865
 - Rectal Neoplasms
 - Ethylene, Trichloro-, 79-5376
 - Respiratory Tract Diseases
 - Suberosis, 79-5367
 - Respiratory Tract Neoplasms
 - Epidemiology, 79-5361, 79-5363
 - Talc, 79-5363
 - Silicosis
 - Epidemiology, Germany, 79-4854
 - Smoking
 - Co-carcinogenic Effect, Review, 79-4807, 79-4830
- ## Ochratoxin A
- Food Contamination
 - Body Fluids, Tissues, Cow, 79-5030
 - Milk, 79-5030

Oncogenic Viruses

- Adenosine Cyclic 3',5' Monophosphate
 - Cell Transformation, Neoplastic, Review, 79-4937
- Adenyl Cyclase
 - Cell Transformation, Neoplastic, Review, 79-4937
- Child

Oncogenic Viruses (cont'd)

- Epidemiology, Review, 79-4815
- Chromosomes
 - Cell Transplantation, Neoplastic, Review, 79-4866
 - Enzyme Induction, Review, 79-4866
 - Hybrid Cells, Review, 79-4916
- Co-carcinogenic Effect
 - Epidemiology, Review, 79-4803
- Histocompatibility Antigens
 - Immunity, Cellular, Review, 79-4902

Orbital Neoplasms

- Sarcoma, Ewing's
 - Case Report, 79-5312

Osteomyelitis

- Carcinoma, Epidermoid
 - Case Report, 79-5319

Ouabain

- Ethylene, Chloro-
 - Mutation, 79-4959

Ovarian Neoplasms

- Adenofibroma
 - Epidemiology, 79-5382
- Brenner Tumor
 - Epidemiology, 79-5380
- Child
 - Epidemiology, Review, 79-4925
- Cystadenocarcinoma
 - Genetics, 79-5347
- Cystadenoma
 - Epidemiology, 79-5382
- Cysts
 - Epidemiology, 79-5382
- Disgerminoma
 - Age Factors, 79-5382
 - Turner's Syndrome, 79-5345
- Fibroma
 - Epidemiology, 79-5380
- Genetics
 - Case Report, 79-5347
- Gonadotropins, Chorionic
 - Endocrine Abnormalities, Review, 79-4850
- Granulosa Cell Tumor
 - Epidemiology, 79-5380
 - Puberty, Precocious, 79-5346
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Leiomyoma
 - Epidemiology, 79-5380
- Neoplasm Metastasis
 - Epidemiology, 79-5380
- Puberty, Precocious
 - Case Report, 79-5346
- Teratoid Tumor
 - Epidemiology, 79-5382
 - Turner's Syndrome, 79-5345
- 12-O-Tetradecanoylphorbol-13-acetate
 - Mouse, Nude, 79-5041
- Theca Cell Tumor
 - Age Factors, 79-5382
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Turner's Syndrome
 - Case Report, 79-5345

2-Oxazolidinone, 3-(5-Nitrofurfurylidine)amino-*Escherichia coli*

- Mutagenic Activity, 79-5000

- Oxygen**
 - Cyclohexylamine
 - Metabolism, 79-4970
- Oxygenases**
 - Dieldrin
 - Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
 - 79-5068
 - Propane, 1,2-Epoxy-3,3,3-trichloro-
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-4965
- Oxymetholone**
 - Hepatoma
 - Histological Study, Review, 79-4847
- Page's Disease, Extra-Mammary**
 - Prostatic Neoplasms
 - Case Report, 79-5352
 - Testicular Neoplasms
 - Adenocarcinoma, 79-5352
- Pancreatic Neoplasms**
 - Adenocarcinoma
 - Neoplasm Metastasis, 79-5302
 - Adenomatosis, Familial Endocrine
 - Case Report, 79-5309
 - Diarrhea, 79-5309
 - Angioma
 - Hippel-Lindau Disease, 79-5303
 - Apudoma
 - Classification, Review, 79-4912
 - Benz(a)anthracene, 7,12-Dimethyl-
 - Carcinogenic Potential, 79-5373
 - Benzidine
 - Occupational Hazard, 79-5373
 - Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 - Carcinogenic Potential, 79-5373
 - Corticotropin
 - Zollinger-Ellison Syndrome, 79-5076
 - Cystadenoma
 - Hippel-Lindau Disease, 79-5303
 - Diabetes Mellitus
 - Epidemiology, France, 79-5373
 - Dipropylamine, 2,2'-Dihydroxy-*N*-nitroso-
 - Carcinogenic Potential, 79-5373
 - Gastrin
 - Corticotropin, 79-5076
 - Gastrointestinal Hormones
 - Diarrhea, 79-5309
 - Hippel-Lindau Disease
 - Case Report, 79-5303
 - Islet Cell Tumor
 - Adenomatosis, Familial Endocrine, 79-5309
 - 2-Naphthylamine
 - Occupational Hazard, 79-5373
 - Neoplasm Metastasis
 - Case Report, 79-5302
 - Occupational Hazard
 - Epidemiology, France, 79-5373
 - Pancreatitis
 - Epidemiology, 79-5372
 - Smoking
 - Epidemiology, France, 79-5373
 - Urea, Methyl Nitroso-
 - Carcinogenic Potential, 79-5373
 - Zollinger-Ellison Syndrome
 - Case Report, 79-5076
- Pancreatitis**
 - Acute Disease
- Pancreatitis (cont'd)**
 - Water Supply, 79-5372
- Pancreatic Neoplasms**
 - Epidemiology, 79-5372
- Pancytopenia**
 - see Anemia, Aplastic
- Panfuran-S**
 - Digestive System Neoplasms
 - Adenocarcinoma, 79-5011
 - Carcinoma, Epidermoid, 79-5011
 - Papilloma, 79-5011
 - Neoplasms, Experimental
 - Dose-Response Study, Mouse, 79-5011
- Papilloma**
 - Antilymphocyte Serum
 - Immunosuppression, 79-5256
 - Benz(a)anthracene, 7,12-Dimethyl-
 - Lipids, 79-5052
 - Benzo(a)pyrene
 - Lipids, 79-5052
 - Dibenz(a,h)acridine
 - Iron Oxide, 79-4947
 - Digestive System Neoplasms
 - 1,2,4-Triazine, 3-(Dihydroxymethyl)amino-6-(5-nitro-2-furylethenyl, 79-5011
 - T-Lymphocytes
 - Antilymphocyte Serum, 79-5256
 - α,β -Mannitose
 - Carcinogenic Potential and Toxicity, Review
 - 79-4831
 - Ribosomes
 - Cell Differentiation, Review, 79-4910
 - Virus, Shope Rabbit Papilloma
 - DNA, Viral, 79-5150
- Paraganglioma**
 - Adrenal Gland Neoplasms
 - Raynaud's Disease, 79-5308
- Paraganglioma, Nonchromaffin**
 - Papilledema
 - Case Report, 79-5315
- Parathyroid Hormone**
 - Melanoma
 - Hyperparathyroidism, 79-5324
- D-Pencillamine**
 - see Valine, 3-Mercapto-
- 4-Pentoic Acid, 2-(Diethylamino)ethyl-2-phenyl-2-(2-propene)-**
 - Diethylamine, *N*-Nitroso-
 - Nucleic Acids, 79-4990
- Peptic Ulcer**
 - Mucosal Junctions
 - Histological Mapping, 79-5336
 - Stomach Neoplasms
 - Gastrectomy, 79-5111
 - Precancerous Conditions, 79-5336
- Peptide Hydrolases**
 - Digestive System Neoplasms
 - Diet, 79-4930
- Peptides**
 - Glucose, 2-Deoxy-
 - Metabolism, 79-5077
 - Virus, Hamster C-Type RNA Tumor
 - Antigenic Determinants, 79-5148

Peptides (cont'd)

- Virus, Herpes Simplex
 - Cell-Free Translation System, 79-4884
- Virus, Herpes Simplex 1
 - DNA, Viral, 79-5189
 - Genes, Viral, 79-5188
 - Virus Replication, Review, 79-4885
- Virus, Herpes Simplex 2
 - DNA, Viral, 79-5189
 - Virus Replication, Review, 79-4885
- Virus, Rous Sarcoma
 - Tunicamycin, 79-5116

Peritoneal Neoplasms

- Adenocarcinoma
 - 12-*O*-Tetradecanoylphorbol-13-acetate, 79-5041
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Mouse, Nude, 79-5041

Peroxidases

- 4,4'-Stilbenediol, α, α' -Diethyl-3,5,3',5'-tetrafluoro-
 - Metabolism, 79-5084

Pesticides

- Environmental Pollutants
 - Quantitation Method, Review, 79-4837
- Nitrosamines
 - Environmental Pollution, Review, 79-4827

Peutz-Jeghers Syndrome

- Polyps
 - Case Report, 79-5305
- Esophagus, 79-5305

Phagocytosis

- Adipose Tissue
 - Hemocytes, 79-5282
- Aflatoxin B1
 - Bacteria, 79-5033
 - Heterophils, Chick, 79-5033
- Neoplasms, Experimental
 - Hemocytes, 79-5282
- Smoking
 - Hydrogen Peroxide, 79-5015
 - Macrophages, 79-5015

Pharyngeal Neoplasms

- Ethyl Alcohol
 - Epidemiology, Review, 79-4919
- Smoking
 - Epidemiology, Review, 79-4919

Phenanthrene

- Diol Epoxides
 - Electronic Structures, 79-5037

Phenethylhydrazine Sulfate

- Nitroso Compounds
 - Drug Contamination, 79-5010

Phenol, (1,1-Dimethylethyl)-4-methoxy-

- Benzo(a)pyrene
 - Aryl Hydrocarbon Hydroxylases, 79-5074

***o*-Phenylenepyrene**

- see Indeno(1,2,3-cd)pyrene

Pheochromocytoma

- Adrenal Gland Neoplasms
 - Raynaud's Disease, 79-5308
- Genetics
 - Case Report, 79-5308
 - Hypertension, 79-5308

Phorbol Esters

- Glucose, 2-Deoxy-
 - Metabolism, 79-5077

Phosphates

- Cyclohexene Oxide
 - Diol Epoxides, 79-4968

Phosphatidylcholines

- Acetamide, *N*-Fluorenyl-2-yl-
 - Membranes, Binding, 79-4985
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 - Membranes, Binding, 79-4985
- Estrone
 - Membranes, Binding, 79-4985
- Testosterone
 - Membranes, Binding, 79-4985
- Virus, Sendai
 - Cell Membrane, 79-5229

Phosphatidylethanolamines

- Macrophages
 - Methyltransferases, 79-5258

Phosphatidylinositols

- Calcium
 - Metabolism, Review, 79-4835
- Cell Membrane
 - Alkaline Phosphatase, 79-4835
 - Cell Cycle Kinetics, Review, 79-4835

Phosphine Oxide, Tris(1-aziridinyl)-

- Mutagenic Activity
 - Mammals, Microorganisms, Review, 79-4835

Phospholipids

- Macrophages
 - Chemotactic Factors, 79-5258
 - Methylation, 79-5258
- Melanoma
 - Metabolism, 79-5399
- Virus, SV40
 - Cell Adhesion, 79-5219

Phosphonoacetic Acid

- Infectious Mononucleosis
 - Virus Replication, 79-5168
- Virus, Epstein-Barr
 - Lymphocyte Transformation, 79-5168
 - Virus Replication, 79-5168
- Virus, Herpes Simplex 1
 - Genes, Viral, 79-5179
- Virus, Visna
 - Virus Replication, 79-5154

Phosphonoformic Acid, Trisodium Salt

- Virus, Visna
 - Reverse Transcriptase, 79-5154
 - Virus Replication, 79-5154

Phosphoproteins

- Virus, Measles
 - Antibodies, Viral, 79-5228

Phosphoric Acid, 2,2-Dichlorovinyl-, Dimethyl Ester

- Mutagenic Activity
 - Mammals, Microorganisms, Review, 79-4835

Phosphoric Acid, Lead Salt

- Kidney Neoplasms
 - Carcinogenic Potential, Review, 79-4814

- Phosphoric Acid, Trimethyl Ester**
 - Chromosome Aberrations
 - Mutagenic Activity, Review, 79-4816
 - Fibroma
 - Carcinogenic Activity, Mouse, Rat, 79-4816
 - Spermatogenesis
 - Mutagenic Activity, Review, 79-4816
 - Uterine Neoplasms
 - Adenocarcinoma, 79-4816
 - Carcinogenic Activity, Mouse, Rat, 79-4816
- Phosphorus**
 - 4,4'-Stilbenediol, α, α' -Diethyl-
 - Mineralization, Kidney, 79-5082
- Phosphotransferases**
 - Lymphoma
 - Isolation and Characterization, 79-5396
 - Pyrimidine, 79-5396
 - as*-Triazine-3,5-(2*H*,4*H*)-dione, 2- β -*D*-Ribofuranosyl-, 79-5396
 - Uracil, 5-Fluoro-, 79-5396
- Photochemotherapy**
 - Fibrosarcoma
 - Transplantation Immunology, 79-5099
- Pinocytosis**
 - Lung Neoplasms
 - Gold, 79-5257
 - Macrophages, 79-5257
- Piperidine, 1-Nitroso-**
 - Food Contamination
 - Carcinogenic Potential, Review, 79-4828
- Pituitary Neoplasms**
 - Adenoma
 - Diet, 79-5397
 - Epidemiology, Rat, 79-5400
 - Neoplasm Metastasis, 79-5298
- Plant Agglutinins**
 - Breast Neoplasms
 - Lymphocyte Transformation, 79-5254
 - Gastrointestinal Neoplasms
 - Lymphocyte Transformation, 79-5254
 - Infectious Mononucleosis
 - Lymphocyte Transformation, 79-5170
 - Radiation, Ionizing
 - Chromosome Aberrations, 79-5101
 - Virus, Epstein-Barr
 - Lymphocyte Transformation, 79-5170
 - Virus, Herpes Simplex 1
 - Lymphocyte Transformation, 79-5181
- Plasmacytoma**
 - Histocompatibility Antigens
 - Cell Differentiation, 79-5264
 - IgM
 - Binding Sites, 79-5265
 - Immunoglobulins, Heavy Chain
 - Amino Acids, 79-5265
 - Carbohydrates, 79-5265
 - Immunoglobulins, Surface
 - Cell Differentiation, 79-5264
 - IgA, 79-5264
 - Melanoma
 - Hybrid Cells, 79-5263
 - Myeloma Proteins
 - Clone Cells, 79-5264
- Plasmacytoma (cont'd)**
 - Viral Proteins
 - Cell Differentiation, 79-5264
 - Virus, Vesicular Stomatitis
 - RNA Replication, 79-5230
- Platinum, Tetrachloro-**
 - Azaguanine Resistance
 - Mutagenic Activity, 79-4949
 - Cobalamine, Methyl-
 - Reaction Products, 79-4949
 - Mutagenic Activity
 - Hamster Ovary Cells, 79-4949
- Plutonium**
 - Radioactive Fallout
 - Anarctica, 79-5098
 - Smoking
 - Co-carcinogenic Effect, 79-4857
 - Tobacco
 - Risk Factors, Review, 79-4857
- Pneumoconiosis**
 - Lung Neoplasms
 - Carcinoma, 79-5371
 - Epidemiology, 79-5371
 - Occupational Hazard
 - Epidemiology, 79-5364
- Pneumonia**
 - Carcinoembryonic Antigen
 - Ascites, Pleural Effusions, 79-5242
- Poikiloderma Congenitale**
 - Carcinoma, Epidermoid
 - Case Report, 79-5269
 - Leukocytes
 - Immune Response, 79-5269
 - B-Lymphocytes
 - Immune Response, 79-5269
- Poly ADP Ribose Polymerase**
 - Virus, Herpes Simplex 1
 - Chromatin, 79-5176
 - DNA Replication, 79-5176
- Polycyclic Hydrocarbons**
 - Air Pollution
 - Spectrum Analysis, 79-5055
 - Aryl Hydrocarbon Hydroxylases
 - Enzyme Induction, Review, 79-4839
 - Cytochrome P-450
 - Metabolism, Review, 79-4840
 - Environmental Hazard
 - Epidemiology, Review, 79-4811
 - Environmental Pollutants
 - Quantitation Method, Review, 79-4837
 - Methionine
 - Amino Acyl T RNA Synthetases, 79-5069
 - RNA, Transfer, 79-5069
 - Structure-Activity Relationship
 - Carcinogenic Metabolite, Review, 79-4920
 - Carcinogenic Potential, Review, 79-4836
- Polycythemia Vera**
 - Leukemia, Myelocytic
 - Chromosomes, Human, 21-22, 79-5292
- Polyps**
 - Bronchial Neoplasms
 - Burns, Inhalation, 79-5108
 - Esophagus

Polyps (cont'd)

- Peutz-Jeghers Syndrome, 79-5305
- Intestinal Neoplasms
 - Adenocarcinoma, 79-4913
 - Precancerous Conditions, Review, 79-4913
- Laryngeal Neoplasms
 - Diethylamine, *N*-Nitroso-, 79-4991
- Peutz-Jeghers Syndrome
 - Case Report, 79-5305
- Rectal Neoplasms
 - Adenocarcinoma, 79-5343
 - Case Report, 79-5343
 - Histological Study, 79-5343
- Stomach Neoplasms
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
- Tracheal Neoplasms
 - Diethylamine, *N*-Nitroso-, 79-4991
- Urethral Neoplasms
 - Case Report, Child, 79-5342
- Uterine Neoplasms
 - Precancerous Conditions, Review, 79-4933

Polyribosomes

- Virus, Herpes Simplex 1
- Proteins, 79-5178

Potassium

- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 79-5227
- Virus, Sindbis
 - Protein Synthesis, 79-5227

Precancerous Conditions

- Bladder Neoplasms
 - Adenocarcinoma, 79-5341
 - Carcinoma, Epidermoid, 79-5341
 - Carcinoma, Transitional Cell, 79-5341
 - Histological Study, Mouse, 79-5341
- Breast Neoplasms
 - Antigens, Viral, 79-5226
- Carcinoma, Basal Cell
 - Diagnosis and Treatment, Review, 79-4862
- Carcinoma, Epidermoid
 - Diagnosis and Treatment, Review, 79-4862
 - Keratoacanthoma, 79-5222
- Cervix Neoplasms
 - Virus, Herpes Simplex 2, 79-5193
- Keratoacanthoma
 - Diagnosis and Treatment, Review, 79-4862
- Laryngeal Neoplasms
 - Smoking, 79-5017, 79-5325
- Leukemia
 - Hematological Diseases, 79-5289
- Leukemia, Lymphoblastic
 - Genetics, 79-5289
- Leukemia, Myeloblastic
 - Alkaline Phosphatase, 79-5291
 - Anemia, Aplastic, 79-5291
 - Bone Marrow, 79-5291
 - Genetics, 79-5289
 - Granulocytes, 79-5291
- Leukemia, Myelocytic
 - Anemia, 79-5293
 - Thrombopenia, 79-5293
- Lung Neoplasms
 - Chromium, 79-4946
- Melanoma
 - Diagnosis and Treatment, Review, 79-4862
- Nose Neoplasms

Precancerous Conditions (cont'd)

- Nickel, 79-4948
- Skin Neoplasms
 - Keratinocytes, 79-5398
- Stomach Neoplasms
 - Epidemiology, 79-5378
 - Gastric Mucosa, 79-5378
 - Metaplasia, 79-5378
 - Peptic Ulcer, 79-5336
 - Ulcers, 79-5378
- Uterine Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5051

Prednisolone

- Chromatids
 - Chromosome Aberrations, 79-4994

Pregn-4-ene-3,20-dione, 17-(Acetyloxy)-6 α -methyl-

- Uterine Neoplasms
 - Epidemiology, 79-5354

Pregnancy

- Breast Neoplasms
 - Epidemiology, 79-5360
 - Epidemiology, Review, 79-4939
 - Immunosuppression, 79-5360
- Leukemia, Lymphoblastic
 - Virus, Varicella-Zoster, 79-5267
- T-Lymphocytes
 - Transplantation Immunology, 79-5235
- Neoplasms, Experimental
 - Transplantation Immunology, 79-5235
- Smoking
 - Growth Retardation, Review, 79-4830
- Virus, Cytomegalo
 - Antibodies, Viral, 79-5175
- Virus, Herpes Simplex
 - Antibodies, Viral, 79-5175

Premarin

- Uterine Neoplasms
 - Epidemiology, 79-5354

Progestational Hormones

- Liver Neoplasms
 - Epidemiology, France, 79-5374
- Uterine Neoplasms
 - Drug Therapy, 79-5089

Progesterone

- Hydroxylases
 - Adrenal Cortex, Rat, 79-5073
- LS 1727
 - Metabolism, 79-5046
- Prolactin
 - Receptors, Hormone, 79-5047
- Serum Levels
 - Ovariectomy, Hypophysectomy, 79-5051

Prolactin

- Breast Neoplasms
 - Menopause, Review, 79-4928
- Cervix Neoplasms
 - Adenocarcinoma, 79-5075
 - Carcinoma, Epidermoid, 79-5075
- Estradiol
 - Receptors, Hormone, 79-5047
- Mammary Neoplasms, Experimental
 - DNA Replication, 79-5047
 - Receptors, Hormone, 79-5047
- Progesterone

- Prolactin (cont'd)**
 Receptors, Hormone, 79-5047
 Reserpine
 Carcinogenic Potential, Review, 79-4849
- Proline**
 2-Pyrrolidine, 1-nitroso-, Acetate (Ester)
 Synthesis, 79-4997
- Proline, 4-Hydroxy-**
 4,4'-Stilbenediol, α,α' -Diethyl-
 Calcium, 79-5082
- Propane, 1,2-Epoxy-**
 Ames Test
 Mutagenic Activity, 79-4964
 Chromosome Aberrations
 Lymphocytes, 79-4964
Escherichia coli
 Mutagenic Activity, 79-4964
 Lymphocytes
 Bone Marrow, 79-4964
- Propane, 1,2-Epoxy-3,3,3-trichloro-**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Oxygenases, 79-4965
 1,1'-Biphenyl, 2,2',4,4'-Tetrachloro-
 Binding, 79-4965
 Microsomes, Liver
 Aminopyrine *N*-Demethylase, 79-4965
 Aryl Hydrocarbon Hydroxylases, 79-4965
- Propane, 2-Nitro-**
 Hepatoma
 Inhalation Study, Rat, 79-4976
- 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate**
 Anisole, Dichloro-*p*-nitro-Demethylases
 Metabolism, Liver, 79-4958
- Prostaglandins**
 Adenosine Cyclic 3',5' Monophosphate
 Graft Rejection, 79-4842
 Graft Rejection
 Immune Response, Review, 79-4842
 Guanosine Cyclic 3',5' Monophosphate
 Graft Rejection, 79-4842
- Prostaglandins E**
 Astrocytoma
 Adenosine Cyclic 3',5' Monophosphate, 79-5072
 Adenyl Cyclase, 79-5072
- Prostatic Neoplasms**
 Adenocarcinoma
 Animal Models, Review, 79-4853
 Carcinogen, Chemical, 79-4853
 Radiation, Ionizing, 79-4853
 Virus, SV40, 79-4853
 Androgens
 Co-carcinogenic Effect, Review, 79-4929
 Animal Models, Review
 Steroids, 79-4853
 Carcinoma
 Diagnosis, 79-5387
 Epidemiology, Sweden, 79-5387
 Dietary Fats
 Epidemiology, Review, 79-4927
 Neoplasms, Multiple Primary
 Epidemiology, 79-5355
 4,4'-Stilbenediol, α,α' -Diethyl-, 79-5083
 Paget's Disease, Extra-Mammary
- Prostatic Neoplasms (cont'd)**
 Case Report, 79-5352
 Virus, Herpes Simplex
 Antigen-Antibody Reactions, 79-5191
- Proteins**
 Chloramphenicol
 Chromosome Abnormalities, 79-5043
 Virus, Herpes Simplex 1
 Immune Serums, 79-5183
 Polyribosomes, 79-5178
- Pseudoepitheliomatous Hyperplasia**
 see Hyperplasia
- Psoralen, 8-Methoxy-**
 T-Lymphocytes
 Immunosuppression, 79-5099
 Photolysis
 Triplet State Properties, 79-5093
 Skin Neoplasms
 Photochemotherapy, Review, 79-4861
 Triplet State Properties
 Spectrum Analysis, 79-5093
 Ultraviolet Rays
 Transplantation Immunology, 79-5099
- Psoriasis**
 Neoplasms, Multiple Primary
 Case Report, 79-5104
 Skin Neoplasms
 Aryl Hydrocarbon Hydroxylases, 79-5277
 Carcinoma, Epidermoid, 79-5104
 Drug Therapy, 79-5104
 Histocompatibility Antigens, 79-5277
 Keratoacanthoma, 79-5104
 Photochemotherapy, Review, 79-4861
 Radiotherapy, 79-5104
 Ultraviolet Rays
 Immune Response, 79-5277
- Puberty, Precocious**
 Ovarian Neoplasms
 Case Report, 79-5346
 Granulosa Cell Tumor, 79-5346
- Pulmonary Adenomatosis, Ovine**
 Virus, Herpes
 Co-carcinogenic Effect, 79-5153
 DNA-RNA Hybridization, 79-5153
 Horizontal Transmission, 79-5153
- Pulmonary Emphysema**
 Chromium
 Occupational Hazard, 79-4946
- Pulmonary Fibrosis**
 Chromium
 Occupational Hazard, 79-4946
- Purine, 2-Amino-6-methoxy-**
 Xeroderma Pigmentosum
 Chromatids, Review, 79-4829
- Purine-6-thiol**
 Chromatids
 Chromosome Aberrations, 79-4994
 Kidney Diseases
 Chromosome Aberrations, 79-4994
- Puromycin**
 Melanoma
 Melanin, 79-5231

Puromycin (cont'd)

- Microsomes, Liver
- DNA Replication, 79-5057

2-Pyrenamine

- Arylnitrenium Ions
- Mutagenic Activity, 79-5038

Pyridazine, 3-Amino-6-(2-(5-nitro-2-furyl)vinyl)-, HCl

- Saccharomyces cerevisiae*
- Mutagenic Activity, 79-5009

Pyridine, 4-((4-Nitrophenyl)methyl)-

- Serine, Diazoacetate (Ester)
- Alkylation, 79-4999

Pyrimidine

- Lymphoma
- Phosphotransferases, 79-5396

Pyrrolidine, 1-Nitroso-

- Food Contamination
- Nitrosamines, 79-4828

2-Pyrrolidine, 1-nitroso-, Acetate (Ester)

- Acetic Acid, Lead Salt
- Synthesis, 79-4997
- Proline
- Synthesis, 79-4997

Pyruvate Kinase

- Virus, Herpes Simplex 1
- Anti-Antibodies, 79-5183

Quartz

- Virus, Moloney Murine Leukemia
- Co-carcinogenic Effect, 79-4943

Quercetin

- see Flavone, 3,3',4',5,7-Pentahydroxy-

Quinoline, 4-(Hydroxyamino)-, 1-Oxide

- Aluminum Chloride
- DNA, Binding, 79-5008
- Nucleotides, Binding, 79-5008
- Blood-Brain Barrier
- Biological Transport, Mouse, 79-5007
- Copper
- DNA, Binding, 79-5008
- DNA, Binding
- Lung, Mouse, 79-5008
- Nervous System
- Tissue Distribution, 79-5007
- Zinc
- DNA, Binding, 79-5008

Quinoline, 4-Nitro-, 1-Oxide

- Blood-Brain Barrier
- Biological Transport, Mouse, 79-5007
- DNA Repair
- Chromatids, Review, 79-4829
- Nervous System
- Tissue Distribution, 79-5007

Radiation, Ionizing

- Aryl Hydrocarbon Hydroxylases
- Cells, Cultured, 79-5100
- Lung, Mouse, 79-5025
- Benz(a)anthracene
- Aryl Hydrocarbon Hydroxylases, 79-5100
- Brain Neoplasms
- Case Report, 79-5102
- Fibrosarcoma, 79-5102

Radiation, Ionizing (cont'd)

- Breast Neoplasms
- Epidemiology, Review, 79-4815
- Chromatids
- Lymphocytes, 79-5101
- Chromosome Aberrations
- Cell Cycle Kinetics, 79-5101
- Fibrosarcoma
- Aryl Hydrocarbon Hydroxylases, 79-5100
- Gastrointestinal Neoplasms
- Epidemiology, 79-5385
- Radiography, 79-5385
- Leukemia
- Epidemiology, Child, 79-5359
- Epidemiology, Review, 79-4815
- Radiography, 79-5385
- Leukemia, Myeloblastic
- Adriamycin, 79-4995
- Case Report, 79-4995
- Cyclophosphamide, 79-4995
- T-Lymphocytes
- Cortisone Acetate, 79-4903
- Suppressor Cells, Review, 79-4903
- Lymphoma
- Immunogenetics, 79-5270
- Mutation
- Genetic Effects, Review, 79-4865
- Genetic Risks, 79-5385
- Occupational Hazard
- Genetic Effects, Review, 79-4865
- Plant Agglutinins
- Chromosome Aberrations, 79-5101
- Prostatic Neoplasms
- Adenocarcinoma, 79-4853
- Sarcoma, Mast Cell
- Immunosuppression, 79-5273
- Thyroid Neoplasms
- Epidemiology, Review, 79-4815
- Uridine, 5-Bromo-2'-deoxy-
- Chromosome Aberrations, 79-5101
- Virus, Epstein-Barr
- Virus Cultivation, 79-5162
- Virus, Herpes Simplex 1
- Immunosuppression, 79-5182
- Virus, Herpes Simplex 2
- Neoplasm Transplantation, 79-5236
- Virus, SV40
- Virus Replication, 79-5209

Radioactive Fallout

- Leukemia
- Epidemiology, Child, 79-5359
- B-Lymphocytes
- Chromosome Aberrations, 79-5096, 79-5097
- T-Lymphocytes
- Chromosome Aberrations, 79-5096
- Plutonium
- Anarctica, 79-5098
- Virus, Epstein-Barr
- Chromosome Aberrations, 79-5096, 79-5097

Radiotherapy

- Brain Neoplasms
- Acromegaly, 79-5102
- Leukemia, Myeloblastic
- Hodgkin's Disease, 79-5103
- Skin Neoplasms
- Psoriasis, 79-5104

- Raynaud's Disease**
 Adrenal Gland Neoplasms
 Paraganglioma, 79-5308
 Pheochromocytoma, 79-5308
- Receptors, Adrenergic**
 Astrocytoma
 Isoproterenol, 79-5072
- Receptors, Estrogen**
 Estradiol
 Uterus, 79-5087
- Receptors, Hormone**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 79-5047
 Prolactin, 79-5047
 Prolactin
 Estradiol, 79-5047
 Progesterone, 79-5047
 4,4'-Stilbenediol, α,α' -Diethyl-
 Leydig Cells, 79-5080
 4,4'-Stilbenediol, α,α' -Diethyl-3,5,3',5'-tetrafluoro-
 Uterus, Mouse, 79-5084
- Rectal Neoplasms**
 Adenocarcinoma
 Polyps, 79-5343
 Ethylene, Trichloro-
 Occupational Hazard, 79-5376
 Polyps
 Case Report, 79-5343
 Histological Study, 79-5343
- Renal Cell Carcinoma**
 see Adenocarcinoma
- Reserpine**
 Breast Neoplasms
 Carcinogenic Potential, Review, 79-4849
 Prolactin
 Carcinogenic Potential, Review, 79-4849
- Respiratory Tract Diseases**
 Occupational Hazard
 Suberosis, 79-5367
- Respiratory Tract Neoplasms**
 Adenoma
 Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 79-4978
 Benzo(a)pyrene
 Agar, 79-4947
 Air Pollution, 79-5366
 Iron Oxide, 79-4947
 Manganese Dioxide, 79-4947
 Silica, 79-4947
 Dibenz(a,h)acridine
 Iron Oxide, 79-4947
 Ethane, 1,2-Dichloro-
 Carcinogenic Activity, Mouse, Rat, 79-4961
 Ethyl Alcohol
 Epidemiology, 79-5356
 Epidemiology, France, 79-4924
 Mesothelioma
 Asbestos, 79-4978
 Occupational Hazard
 Epidemiology, 79-5361, 79-5363
 Smoking
 Epidemiology, France, 79-4924
 Epidemiology, Review, 79-4830
- Respiratory Tract Neoplasms (cont'd)**
 Talc
 Occupational Hazard, 79-5363
 Tars
 Epidemiology, 79-5366
- Reticuloendotheliosis**
 Histiocytosis X
 Case Report, Infant, 79-5284
- Retinoblastoma**
 Child
 Epidemiology, Review, 79-4925
- Retinoic Acid**
 Bladder Neoplasms
 Cell Differentiation, 79-5395
 Cell Migration Inhibition, 79-5395
 DNA Replication, 79-5395
 Keratin, 79-5395
- 13-*cis*-Retinoic Acid**
 Bladder Neoplasms
 Carcinogen, Chemical, 79-4846
- Reverse Transcriptase**
 Virus, Hamster C-Type RNA Tumor
 Isolation and Characterization, 79-5147
 RNA, Viral, 79-5148
 Viral Proteins, 79-5147
 Virus, Moloney Murine Leukemia
 Cations, Divalent, 79-5132
 Virus, Rauscher Murine Leukemia
 Attenuated Virus, 79-5138
 Virus, Rous-Associated
 Phenotype, 79-5118
 Virus, Visna
 Phosphonoformic Acid, Trisodium Salt, 79-5154
- Rhabdomyosarcoma**
 Child
 Epidemiology, Review, 79-4925
 Cobalt
 Cortisol, 79-5070
 Cortisol
 Proteins, Metabolism, 79-5070
 RNA, Transfer, Methyltransferases, 79-5070
 DNA
 Synovioma, 79-5224
- Rheumatic Fever**
 Leukemia, Lymphoblastic
 Autoimmune Diseases, 79-5267
- Rheumatoid Factor**
 Sarcoma, Reticulum Cell
 IgA, 79-5272
- Ribonucleoproteins**
 Sarcoma, Reticulum Cell
 IgG, 79-5297
- Ribosomes**
 Hyperplasia
 Epidermis, Review, 79-4910
 Papilloma
 Cell Differentiation, Review, 79-4910
- RNA**
 Antigens
 Immunity, Cellular, 79-5234
 Histocompatibility Antigens
 Immunity, Cellular, 79-5234

RNA (cont'd)

- Hypersensitivity, Delayed
 - Immunity, Cellular, 79-5234
- Lymphokines
 - Immunity, Cellular, 79-5234
- Macrophages
 - Cell Migration Inhibition, 79-5234

RNA, Messenger

- Cervix Neoplasms
 - Virus, Herpes Simplex 2, 79-5193
- Virus, Adeno
 - Virus Serotype, 79-5202
- Virus, Adeno 3
 - DNA-RNA Hybridization, 79-5202
 - Nucleotide Sequence, 79-5202
- Virus, Adeno 7
 - DNA-RNA Hybridization, 79-5202
 - Nucleotide Sequence, 79-5202
- Virus, Adeno 2 - SV40 Hybrid
 - Antigens, Neoplasm, 79-5199
- Virus, Epstein-Barr
 - DNA Replication, Review, 79-4868
- Virus, Herpes Simplex
 - Cell-Free Translation System, 79-4884
 - DNA Replication, Review, 79-4868
- Virus, Herpes Simplex 1
 - DNA, Viral, 79-5177
- Virus, Polyoma
 - DNA Replication, 79-5204
 - Nucleotide Sequence, 79-5204
 - Viral Proteins, 79-5204
- Virus, Sindbis
 - Protein Synthesis, 79-5227
- Virus, SV40
 - Antigens, Neoplasm, 79-5211, 79-5214
 - Viral Proteins, 79-5211
- Virus, Vesicular Stomatitis
 - Interferon, 79-5227
 - Ultraviolet Rays, 79-5230

RNA Polymerase

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - Enzyme Inactivation, 79-4986
- Virus, Bovine Parvo
 - RNA Replication, 79-5155

RNA Replication

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - Liver, Rat, 79-4986
- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Liver, Rat, 79-4986
- Aryl Hydrocarbon Hydroxylases
 - Enzyme Induction, Review, 79-4839
- Plasmacytoma
 - Virus, Vesicular Stomatitis, 79-5230
- Virus, Adeno 12
 - α -Amanitine, 79-5201
- Virus, Bovine Parvo
 - α -Amanitine, 79-5155
 - RNA Polymerase, 79-5155
- Virus, Vesicular Stomatitis
 - Ultraviolet Rays, 79-5230

RNA, Ribosomal

- Virus, SV40
 - s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-79-5210

RNA, Transfer

- Methionine
 - Polycyclic Hydrocarbons, 79-5069

RNA, Transfer, Methyltransferases

- Rhabdomyosarcoma
 - Cortisol, 79-5070

RNA, Viral

- Virus, Adeno 12
 - Nucleotide Sequence, 79-5201
 - Virus Replication, 79-5201
- Virus, Adeno 2 - SV40 Hybrid
 - Virus, SV40, 79-5199
- Virus, Feline Sarcoma
 - DNA-RNA Hybridization, 79-5151
 - Nucleotide Sequence, 79-5151
- Virus, Friend Murine Leukemia
 - DNA-RNA Hybridization, 79-5130
 - Virus, Friend Spleen Focus-Forming, 79-5130
- Virus, Friend Spleen Focus-Forming
 - Virus, Helper, 79-5130
- Virus, Hamster C-Type RNA Tumor
 - Reverse Transcriptase, 79-5148
- Virus, Rauscher Murine Leukemia
 - Attenuated Virus, 79-5138
- Virus, SV40
 - s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-79-5210

Saccharomyces cerevisiae

- Acetic Acid, (2,4,5-Trichlorophenoxy)-
 - Mutagenic Activity, Review, 79-4832
- Aminoglycosides
 - Mutagenic Activity, 79-5012
- DNA Repair
 - Mutation, 79-4953
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Mutagenic Activity, 79-5009
- Hydantoin, 1-((5-Nitrofurfurylidene)amino)-
 - Mutagenic Activity, 79-5009
- Methanesulfonic Acid, Ethyl Ester
 - DNA Repair, 79-4953
- Methanesulfonic Acid, Methyl Ester
 - DNA Repair, 79-4953
- Pyridazine, 3-Amino-6-(2-(5-nitro-2-furyl)vinyl)-, HCl
 - Mutagenic Activity, 79-5009
- Ultraviolet Rays
 - Mutation, 79-4953

Safrole

- see Benzene, 4-Allyl-1,2-(methylenedioxy)-

Salivary Gland Neoplasms

- Carcinoma
 - Cellular Inclusions, 79-5013
 - Nicotine, 1'-Demethyl-1'-nitroso-, 79-5013
 - Nicotine, 1'-Demethyl-1'-nitroso-
 - Ultrastructural Study, Mouse, 79-5013

Salmonella typhimurium

- Dimethylamine, *N*-Nitroso-
 - Host-Mediated Assay, 79-4988
 - Mutation, 79-4988
- Nitrous Acid, Sodium Salt
 - Metabolism, 79-4974

Sarcoma

- Asbestos
 - Ultrastructural Study, Milk Spots, 79-4943
- Benz(a)anthracene, 7,12-Dimethyl-

- Sarcoma (cont'd)**
 Lipids, 79-5052
 Cholanthrene, 3-Methyl-
 Axilla, Groin, Mouse, 79-5053
 Histocompatibility Antigens, 79-5248
 Immunosuppression, 79-5053
 Clostridiopeptidase A
 Enzymatic Activity, 79-5317
 Complement
 Lymphocytotoxicity, 79-5237
 Heart Neoplasms
 Case Report, 79-5320
 Heart Enlargement, 79-5320
 Histocompatibility Antigens
 Neoplasm Transplantation, 79-5248
 Lung Neoplasms
 Benzo(a)pyrene, 79-5018
 Skin Neoplasms
 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
 Virus, Moloney Murine Leukemia
 Asbestos, 79-4943
- Sarcoma, Ewing's**
 Child
 Epidemiology, Review, 79-4925
 Orbital Neoplasms
 Case Report, 79-5312
- Sarcoma, Immunoblastic**
 see Sarcoma, Reticulum Cell
- Sarcoma, Kaposi's**
 Hodgkin's Disease
 Immunosuppression, Review, 79-4906
- Sarcoma, Mast Cell**
 Histocompatibility Antigens
 Killer Cells, 79-5244
 Immunosuppression
 Antigen-Antibody Reactions, 79-5273
 Neoplasm Transplantation
 Antigen-Antibody Reactions, 79-5273
 Radiation, Ionizing
 Immunosuppression, 79-5273
 Ultraviolet Rays
 Immunosuppression, 79-5273
- Sarcoma, Osteogenic**
 Child
 Epidemiology, Review, 79-4925
- Sarcoma, Reticulum Cell**
 Cellular Inclusions
 IgG, 79-5297
 Immunoglobulins, Light Chain, 79-5297
 Cyroglobulins
 IgA, 79-5272
 IgG, 79-5272
 B-Lymphocytes
 Case Report, 79-5297
 Nasopharyngeal Neoplasms
 Diagnosis, 79-5322
 Rheumatoid Factor
 IgA, 79-5272
 Ribonucleoproteins
 IgG, 79-5297
 Sjogren's Syndrome
 Case Report, 79-5272
 Stomach Neoplasms
 Epidemiology, 79-5377
- Schistosoma japonicum**
 Colonic Neoplasms
 Carcinoma, Mucinous, 79-5339
- Schizophrenia**
 Lung Neoplasms
 Epidemiology, 79-5370
- Scleroderma, Systemic**
 Esophageal Neoplasms
 Carcinoma, Epidermoid, 79-5333
 Case Report, 79-5333
- Sebaceous Gland Neoplasms**
 Ethylene, Chloro-
 Carcinogenic Activity, Review, 79-4808
- Selenic Acid, Dipotassium Salt**
 Carcinoma, Ehrlich Tumor
 Growth, 79-4950
- Selenious Acid, Disodium Salt**
 Carcinoma, Ehrlich Tumor
 Growth, 79-4950
- Selenium**
 Ascorbic Acid
 Metabolism, Review, 79-4844
 Vitamin E
 Metabolism, Review, 79-4844
- Selenium Dioxide**
 Carcinoma, Ehrlich Tumor
 Growth, 79-4950
- Serine, Diazoacetate (Ester)**
 DNA Repair
 Cells, Cultured, 79-4999
 Norleucine, 6-Diazo-5-oxo-
 Alkylation, 79-4999
 Pyridine, 4-((4-Nitrophenyl)methyl)-
 Alkylation, 79-4999
- Sex Chromosome**
 Lung Neoplasms
 Adenocarcinoma, 79-5327
 Chromosome Aberrations, 79-5327
- Sialoglycoproteins**
 Virus, SV40
 Isolation and Characterization, 79-5218
- Silica**
 Benzo(a)pyrene
 Adsorption, Review, 79-4810
 Respiratory Tract Neoplasms
 Benzo(a)pyrene, 79-4947
- Silicosis**
 Occupational Hazard
 Epidemiology, Germany, 79-4854
- Silver Sulfadiazine**
 Ames Test
 Mutagenic Activity, 79-4954
- Sjogren's Syndrome**
 Sarcoma, Reticulum Cell
 Case Report, 79-5272
- Skin Neoplasms**
 Benz(a)anthracene, 7,12-Dimethyl-
 Antilymphocyte Serum, 79-5256
 Lipids, 79-5052
 12-O-Tetradecanoylphorbol-13-acetate, 79-5256

Skin Neoplasms (cont'd)

- Benzo(a)pyrene
 - Lipids, 79-5052
- Carcinoma, Epidermoid
 - Epidemiology, 79-5390
 - Neoplasm Metastasis, 79-5390
 - Psoriasis, 79-5104
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- Cell Membrane Permeability
 - Keratinocytes, 79-5398
- Cholanthrene, 3-Methyl-
 - Lipids, 79-5052
- Dibenz(a,h)anthracene
 - Lipids, 79-5052
- Diet
 - Restriction, 79-5397
- Hyperplasia
 - Virus, Herpes, 79-4881
- Keratoacanthoma
 - Psoriasis, 79-5104
- Neoplasms, Multiple Primary
 - Ultrastructural Study, 79-5321
- Precancerous Conditions
 - Keratinocytes, 79-5398
- Psoralen, 8-Methoxy-
 - Photochemotherapy, Review, 79-4861
- Psoriasis
 - Aryl Hydrocarbon Hydroxylases, 79-5277
 - Drug Therapy, 79-5104
 - Histocompatibility Antigens, 79-5277
 - Photochemotherapy, Review, 79-4861
 - Radiotherapy, 79-5104
- Sarcoma
 - 12-O-Tetradecanoylphorbol-13-acetate, 79-5041
- 12-O-Tetradecanoylphorbol-13-acetate
 - Mouse, Nude, 79-5041
- Ultraviolet Rays
 - Diagnosis and Treatment, Review, 79-4862
- Virus, Herpes
 - Fish, Review, 79-4881

Smoke Condensate

- Cannabis
 - Ames Test, 79-5014
- Lung Neoplasms
 - Methane, Nitro-, 79-5018

Smoking

- Asbestos
 - Co-carcinogenic Effect, 79-5369
 - Co-carcinogenic Effect, Review, 79-4815, 79-4830
- Bladder Neoplasms
 - Epidemiology, 79-5389
- Bronchial Neoplasms
 - Precancerous Conditions, Review, 79-4845
- Esophageal Neoplasms
 - Epidemiology, France, 79-4924
 - Epidemiology, Review, 79-4919
- Ethyl Alcohol
 - Co-carcinogenic Effect, Review, 79-4919
- Head and Neck Neoplasms
 - Neoplasms, Multiple Primary, 79-5355
- Hydrogen Peroxide
 - Phagocytosis, 79-5015
- Laryngeal Neoplasms
 - Animal Model, Hamster, 79-5017
 - Epidemiology, 79-5365
 - Epidemiology, Review, 79-4919

Smoking (cont'd)

- Histological Study, 79-5365
- Precancerous Conditions, 79-5017, 79-5325
- Lip Neoplasms
 - Epidemiology, Review, 79-4830
- Lung Neoplasms
 - Adenocarcinoma, 79-5368
 - Carcinoma, 79-5371
 - Carcinoma, Epidermoid, 79-5368
 - Carcinoma, Oat Cell, 79-5368
 - Epidemiology, Malaysia, 79-5368
 - Epidemiology, Review, 79-4830
 - Tuberculosis, Pulmonary, 79-5328
- Macrophages
 - Glutathione Peroxidase, 79-5015
 - Phagocytosis, 79-5015
 - Superoxide Dismutase, 79-5015
- Melanoma
 - Immune Response, 79-5016
 - Neoplasm Metastasis, 79-5016
- Nicotine
 - Epidemiology, Review, 79-4830
 - Precancerous Conditions, Review, 79-4845
- Occupational Hazard
 - Co-carcinogenic Effect, Review, 79-4807, 79-4830
- Pancreatic Neoplasms
 - Epidemiology, France, 79-5373
- Pharyngeal Neoplasms
 - Epidemiology, Review, 79-4919
- Plutonium
 - Co-carcinogenic Effect, 79-4857
- Pregnancy
 - Growth Retardation, Review, 79-4830
- Respiratory Tract Neoplasms
 - Epidemiology, France, 79-4924
 - Epidemiology, Review, 79-4830
- Tars
 - Precancerous Conditions, Review, 79-4845
- Uranium
 - Co-carcinogenic Effect, Review, 79-4830

Sodium

- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 79-5227
- Virus, Sindbis
 - Protein Synthesis, 79-5227

Sodium Azide

- Ames Test
 - Mutagenic Activity, 79-5005

Soft Tissue Neoplasms

- Virus, Bovine Papilloma
 - DNA, Viral, 79-5156

Sorbic Acid

- Clostridium botulinum*
 - Spore Germination, 79-4975

Spermatogenesis

- Phosphoric Acid, Trimethyl Ester
 - Mutagenic Activity, Review, 79-4816

Spermatozoa

- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-
 - Chromosome Aberrations, 79-4960
- Nitrogen Monoxide
 - Chromosome Aberrations, 79-4960

Spinal Cord Neoplasms

- Neurilemmoma

- Spinal Cord Neoplasms (cont'd)**
Case Report, 79-5314
Neoplasms, Multiple Primary, 79-5314
- Splenic Neoplasms**
Angiosarcoma
12-*O*-Tetradecanoylphorbol-13-acetate, 79-5041
12-*O*-Tetradecanoylphorbol-13-acetate
Mouse, Nude, 79-5041
- Stannane, Chlorotriethyl-
*Escherichia coli***
Antibacterial Activity, 79-5092
- Stannane, Chlorotripropyl-
Acetic Acid, (Ethylenedinitrilo)tetra-
Antibacterial Activity, 79-5092
Escherichia coli
Antibacterial Activity, 79-5092**
- Stannane, Tributylchloro-
Acetic Acid, (Ethylenedinitrilo)tetra-
Antibacterial Activity, 79-5092
Escherichia coli
Antibacterial Activity, 79-5092**
- Steroids**
Prostatic Neoplasms
Animal Models, Review, 79-4853
- 4,4'-Stilbenediol, α,α' -Diethyl-
Abnormalities
Reproductive Dysfunction, Review, 79-4921**
- Ames Test**
Derivatives, 79-5078
Mutagenic Activity, 79-5078
- Aroclor 1254**
Ames Test, 79-5078
- Butyric Acid, 4-Bromo-, Ethyl Ester**
Carboxypropyl Derivative, 79-5081
- Calcium**
Alkaline Phosphatase, 79-5082
Bone Resorption, 79-5082
Proline, 4-Hydroxy-, 79-5082
- Gynecologic Neoplasms**
Epidemiology, Review, 79-4931
- Histamine**
Amide Derivative, 79-5081
- Kidney Neoplasms**
Adenocarcinoma, 79-5083
Case Report, 79-5083
- Leydig Cells**
Receptors, Hormone, 79-5080
- Magnesium**
Mineralization, Kidney, 79-5082
- Phosphorus**
Mineralization, Kidney, 79-5082
- Prostatic Neoplasms**
Neoplasms, Multiple Primary, 79-5083
- Testosterone**
Metabolism, Mouse, 79-5080
- Transplacental Carcinogenesis**
Epidemiology, Review, 79-4815
- 4,4'-Stilbenediol, α,α' -Diethyl-, Bis(dihydrogen phosphate)
Chromosome Aberrations
Bone Marrow, 79-5079**
- 4,4'-Stilbenediol, α,α' -Diethyl-3,5,3',5'-tetrafluoro-
Peroxidases
Metabolism, 79-5084**
- 4,4'-Stilbenediol, α,α' -Diethyl-3,5,3',5'-tetrafluoro- (cont'd)
Receptors, Hormone
Uterus, Mouse, 79-5084**
- Stomach Neoplasms**
Adenocarcinoma
Gastrectomy, 79-5111
Benzene, 4-Allyl-1,2-(methylenedioxy)-
Carcinogenic Potential, Mouse, 79-5023
Benzene, 1,2-(Methylenedioxy)-4-propenyl-
Carcinogenic Potential, Mouse, 79-5023
Carcinoma
Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
Case Report, Heterotropic Pancreas, 79-5335
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
Carcinoma, Epidermoid
Ethane, 1,2-Dichloro-, 79-4961
Cimetidine
Case Report, 79-5040
Dose-Response Study, Rat, 79-5039
Diet
Epidemiology, Review, 79-4926
Epidemiology, Review
Carcinogenic Metabolite, Review, 79-4927
Ethane, 1,2-Dichloro-
Carcinogenic Activity, Mouse, Rat, 79-4961
Gastrectomy
Diagnosis and Prognosis, 79-5111
Peptic Ulcer, 79-5111
Gastric Mucosa
Precancerous Conditions, 79-5378
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Histological Study, Mouse, 79-5001
Hodgkin's Disease
Epidemiology, 79-5377
Hyperplasia
Benzene, 1,2-(Methylenedioxy)-4-propyl-, 79-5023
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
Lymphosarcoma
Epidemiology, 79-5377
Mass Screening
Epidemiology, 79-5379
Metaplasia
Precancerous Conditions, 79-5378
Mucosal Junctions
Histological Mapping, 79-5336
Neoplasm Invasiveness
Epidemiology, 79-5379
Peptic Ulcer
Precancerous Conditions, 79-5336
Polyps
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-5001
Precancerous Conditions
Epidemiology, 79-5378
Sarcoma, Reticulum Cell
Epidemiology, 79-5377
Ulcers
Precancerous Conditions, 79-5378
- Stress, Psychological**
Neoplasms
Immune Response, Review, 79-4934
- Strontium**
D-Gluconic Acid, Strontium Salt
Serum Levels, 79-4951

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Strontium Gluconate
see *D*-Gluconic Acid, Strontium Salt

Succinate Dehydrogenase
Virus, Rous Sarcoma
Fibroblasts, 79-5227

Superoxide Dismutase
Smoking
Macrophages, 79-5015
Toluene-2,4-diamine
Proteins, Binding, 79-5022

Surface-Active Agents
Environmental Pollutants
Quantitation Method, Review, 79-4837

Sweat Gland Neoplasms
Abnormalities
Fingers, Toes, 79-5321
Neoplasms, Multiple Primary
Ultrastructural Study, 79-5321

Synovioma
DNA
Cell Division, 79-5224
Rhabdomyosarcoma
DNA, 79-5224

Talc
Respiratory Tract Neoplasms
Occupational Hazard, 79-5363

Tars
Bladder Neoplasms
Tobacco, 79-5389
Carcinogen, Chemical
Occupational Hazard, Review, 79-4813
Respiratory Tract Neoplasms
Epidemiology, 79-5366
Smoking
Precancerous Conditions, Review, 79-4845

Teratocarcinoma
see Teratoid Tumor

Teratogens
Chemical Reactivity
Quantum Mechanics, Review, 79-4915

Teratoid Tumor
Antigens, Neoplasm
Glycolipids, 79-5262
Immunoprecipitation, 79-5262
Chloramphenicol
Genetics, 79-5391
Glycoproteins
Antigens, Neoplasm, 79-5262
Hyperthyroidism
Endocrine Abnormalities, Review, 79-4855
Hypoxanthine Phosphoribosyltransferase
Genetics, 79-5391
Ovarian Neoplasms
Epidemiology, 79-5382
Turner's Syndrome, 79-5345
Testicular Neoplasms
Epidemiology, Jamaica, 79-5388
Gonadotropins, 79-4855
Histocompatibility Antigens, 79-5249

Testicular Neoplasms
Adenocarcinoma
Paget's Disease, Extra-Mammary, 79-5352

Testicular Neoplasms (cont'd)

Child
Epidemiology, Review, 79-4925
Choriocarcinoma
Gonadotropins, 79-4855
Diet
Restriction, 79-5397
Disgerminoma
Epidemiology, Jamaica, 79-5388
Gonadotropins, 79-4855
Epidemiology
Rat, 79-5400
Gonadotropins, Chorionic
Endocrine Abnormalities, Review, 79-4850
Granulosa Cell Tumor
Estrogens, 79-4855
Gonadotropins, 79-4855
Gynecomastia
Endocrine Abnormalities, Review, 79-4855
Histocompatibility Antigens
Neoplasm Metastasis, 79-5249
Leydig Cell Tumor
Epidemiology, Jamaica, 79-5388
Gonadotropins, 79-4855
Lymphosarcoma
Epidemiology, Jamaica, 79-5388
Teratoid Tumor
Epidemiology, Jamaica, 79-5388
Gonadotropins, 79-4855
Histocompatibility Antigens, 79-5249

Testosterone

Carrier Proteins
Cell Membrane, 79-4985
Cholesterol
Membranes, Binding, 79-4985
Hepatoma
Histological Study, Review, 79-4847
Phosphatidylcholines
Membranes, Binding, 79-4985
4,4'-Stilbenediol, α,α' -Diethyl-
Metabolism, Mouse, 79-5080

12-O-Tetradecanoylphorbol-13-acetate

Chromosomes
Mitosis, Review, 79-4838
Glucose, 2-Deoxy-
Metabolism, 79-5077
Hepatoma
Mouse, Nude, 79-5041
Liver Neoplasms
Hemangioma, 79-5041
Mouse, Nude, 79-5041
Myxosarcoma
Mouse, Nude, 79-5041
Ovarian Neoplasms
Granulosa Cell Tumor, 79-5041
Mouse, Nude, 79-5041
Theca Cell Tumor, 79-5041
Peritoneal Neoplasms
Adenocarcinoma, 79-5041
Mouse, Nude, 79-5041
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 79-5256
Carcinoma, Epidermoid, 79-5041
Mouse, Nude, 79-5041
Sarcoma, 79-5041
Splenic Neoplasms

12-O-Tetradecanoylphorbol-13-acetate (cont'd)

Angiosarcoma, 79-5041

Mouse, Nude, 79-5041

Thyroid Neoplasms

Angiosarcoma, 79-5041

Virus, SV40

DNA Replication, 79-5216

Theca Cell Tumor

Ovarian Neoplasms

Age Factors, 79-5382

12-O-Tetradecanoylphorbol-13-acetate, 79-5041

Thiazole, 2-Amino-4-(5-nitro-2-furyl)-

DNA Repair

Escherichia coli, 79-5000*Escherichia coli*

Mutagenic Activity, 79-5000

Thorium Dioxide

Liver Neoplasms

Case Report, 79-5110

Cholangioma, 79-5110

Hemangioendothelioma, 79-5110

Thrombocytosis

Anemia, Aplastic

Chromosome Aberrations, 79-5288

Thrombopenia

Leukemia, Myelocytic

Precancerous Conditions, 79-5293

Thymidine Kinase

Virus, Herpes Simplex

DNA, Viral, 79-4871

Virus, Herpes Simplex 1

Antibody Specificity, 79-5191

Cell Transformation, Neoplastic, 79-5180

Enzymatic Activity, 79-5180

Genes, Viral, 79-5179, 79-5180

Nucleotide Sequence, 79-5188

Virus, Herpes Simplex 2

Antibody Specificity, 79-5191

Thymus Gland

Abnormalities

Rat, Nude, 79-5259

Thymus Neoplasms

Diet

Restriction, 79-5397

Thyroid Gland

Methane, Nitro-

Organ Weight, 79-4976

Thyroid Neoplasms

Adenoma

Hyperthyroidism, 79-5301

Angiosarcoma

12-O-Tetradecanoylphorbol-13-acetate, 79-5041

Carcinoma

Hereditary Diseases, 79-5299

Hyperparathyroidism, 79-5300

Hodgkin's Disease

Immunosuppression, Review, 79-4906

Hyperparathyroidism

Case Report, 79-5300

Hyperplasia

Calcitonin, 79-5300

Hyperthyroidism

Thyroid Neoplasms (cont'd)

Plummer's Disease, 79-5301

Plummer's Disease

Epidemiology, 79-5301

Radiation, Ionizing

Epidemiology, Review, 79-4815

Sipple's Syndrome

Case Report, 79-5299

Ultrastructural Study, 79-5299

Transplacental Carcinogenesis

Epidemiology, Review, 79-4815

Thyroxine

Methane, Nitro-

Serum Levels, 79-4976

Tobacco

Bladder Neoplasms

Tars, 79-5389

Cadmium

Heavy Metal Levels, 79-4944

Risk Factors, 79-4944

Chromium

Heavy Metal Levels, 79-4944

Copper

Heavy Metal Levels, 79-4944

Iron

Heavy Metal Levels, 79-4944

Lead

Heavy Metal Levels, 79-4944

Manganese

Heavy Metal Levels, 79-4944

Plutonium

Risk Factors, Review, 79-4857

Zinc

Heavy Metal Levels, 79-4944

Toluene-2,4-diamine

Barbituric Acid, 5-Ethyl-5-phenyl-

Ames Test, 79-5022

5,6-Benzoflavone

Ames Test, 79-5022

Deuterium

Mutagenic Activity, 79-5022

Glutathione

Proteins, Binding, 79-5022

Superoxide Dismutase

Proteins, Binding, 79-5022

Tonsillitis

Virus, Epstein-Barr

Antigens, Viral, 79-5171

Tracheal Neoplasms

Carcinoma, Epidermoid

Case Report, 79-5107

Tracheotomy, 79-5107

Diethylamine, N-Nitroso-

Dose-Response Study, Hamster, 79-4991

Polyps

Diethylamine, N-Nitroso-, 79-4991

Transformation, Genetic

Leukemia, Myeloblastic

DNA, 79-5224

Virus, RNA Tumor, 79-5224

Virus, Polyoma

Fibroblasts, 79-5208

Virus, Rous Sarcoma

DNA, Viral, 79-5115

Transplantation, Heterologous

- Carcinoma, Basal Cell
 - Histological Study, 79-5271
 - Mouse, Nude, 79-5271
- Glioma
 - Urea, Ethyl Nitroso-, 79-4979
- Kidney Neoplasms
 - Adenocarcinoma, 79-5280
- Neuroblastoma
 - Mouse, Nude, 79-5304

Transplantation, Homologous

- Cyclosporin A
 - Immune Response, Review, 79-4904
- Fibrosarcoma
 - Neoplasm Invasiveness, 79-5285
- Neoplasms, Experimental
 - Fibroblasts, 79-5285

Transplantation Immunology

- Adenocarcinoma
 - Histocompatibility Antigens, 79-5246
- Bladder Neoplasms
 - Histocompatibility Antigens, 79-4992
- Fibrosarcoma
 - Photochemotherapy, 79-5099
- Histocompatibility Antigens
 - B-Lymphocytes, 79-5246
 - Macrophages, 79-5246
- T-Lymphocytes
 - Pregnancy, 79-5235
- Lymphosarcoma
 - Mouse, Nude, 79-5271
- Neoplasms, Experimental
 - Autoantibodies, 79-5274
 - Cholanthrene, 3-Methyl-, 79-5235
 - Pregnancy, 79-5235
 - Suppressor Cells, Review, 79-4903
- Ultraviolet Rays
 - Psoralen, 8-Methoxy-, 79-5099
- Virus, Herpes Simplex 1
 - Histocompatibility Antigens, 79-5184
- Virus, Marek's Disease Herpes
 - Freund's Adjuvant, 79-5122
 - Glutaraldehyde, 79-5122
 - Histocompatibility Antigens, 79-5121

Trauma

- see Wounds and Injuries

s-Triazin-2(1H)-one, 4-Amino-1-β-D-ribofuranosyl-

- Virus, Kirsten Murine Sarcoma
 - Virus Replication, 79-5143
- Virus, SV40
 - RNA, Ribosomal, 79-5210
 - RNA, Viral, 79-5210

as-Triazine-3,5-(2H,4H)-dione, 2-β-D-Ribofuranosyl-

- Lymphoma
 - Phosphotransferases, 79-5396

s-Triazine, 2,4,6-Tris(1-aziridinyl)-

- Mutagenic Activity
 - Mammals, Microorganisms, Review, 79-4835

Triazines

- Structure-Activity Relationship
 - Electronic Delocalization, 79-4987

Triaziquone

- see *p*-Benzoquinone, 2,3,5-Tris(1-aziridinyl)-

Tributyltin Chloride

- see Stannane, Tributylchloro-

Triethyltin Chloride

- see Stannane, Chlorotriethyl-

Triphenylene

- Ames Test
- Food Contamination, 79-5066

Tripropyltin Chloride

- see Stannane, Chlorotripropyl-

Triton X 100

- Virus, Herpes Simplex 1
 - Cell Membrane Permeability, 79-5185
- Virus, Sendai
 - Membrane Proteins, 79-5229

Tryptophan

- Bladder Neoplasms
 - Co-carcinogenic Effect, Review, 79-4864

Tuberculin

- Virus, Herpes Simplex 1
 - Lymphocyte Transformation, 79-5181

Tuberculosis, Pulmonary

- Lung Neoplasms
 - Adenocarcinoma, 79-5328
 - Carcinoma, Epidermoid, 79-5328
 - Smoking, 79-5328

Tunicamycin

- Virus, Rous Sarcoma
 - Glycoproteins, 79-5116
 - Peptides, 79-5116

Turner's Syndrome

- Ovarian Neoplasms
 - Case Report, 79-5345
 - Disgerminoma, 79-5345
 - Teratoid Tumor, 79-5345

Ulcers

- Stomach Neoplasms
 - Precancerous Conditions, 79-5378

Ultraviolet Rays

- Brain Neoplasms
 - DNA Repair, 79-5200
- Dibenzo-*p*-dioxin, 1,2,3,6,7,8-Hexachloro-
 - Tetra and Penta Isomers, 79-5094
- Dibenzo-*p*-dioxin, 1,2,3,7,8,9-Hexachloro-
 - Tetra and Penta Isomers, 79-5094
- DNA Repair
 - Chromatids, Review, 79-4829
- DNA Replication
 - Photobiology, Review, 79-4856
- T-Lymphocytes
 - Immunosuppression, 79-5099
- Mutation
 - Saccharomyces cerevisiae*, 79-4953
- Psoralen, 8-Methoxy-
 - Transplantation Immunology, 79-5099
- Psoriasis
 - Immune Response, 79-5277
- Sarcoma, Mast Cell
 - Immunosuppression, 79-5273
- Skin Neoplasms

- Ultraviolet Rays (cont'd)**
 Diagnosis and Treatment, Review, 79-4862
 Virus, Herpes
 Virus Activation, Review, 79-4880
 Virus, Mason-Pfizer Monkey
 Cell Fusion, 79-5157
 Virus, Moloney Murine Sarcoma
 Temperature Sensitive Mutants, 79-5134
 Virus, Vesicular Stomatitis
 RNA, Messenger, 79-5230
 RNA Replication, 79-5230
 Viral Proteins, 79-5230
- Uracil, 5-Fluoro-**
 Lymphoma
 Phosphotransferases, 79-5396
- Uranium**
 Dental Prosthesis
 Risk Factors, Review, 79-4857
 Lung Neoplasms
 Occupational Hazard, 79-5369
 Smoking
 Co-carcinogenic Effect, Review, 79-4830
- Urea, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitroso-**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 79-5046
- Urea, 3-(p-Chlorophenyl)-1,1-dimethyl-**
 Chromosome Aberrations
 Hordeum vulgare, 79-4972
- Urea, Ethyl Nitroso-**
 Abnormalities
 Ependyma, Rat, 79-4980
 Brain Neoplasms
 Ultrastructural Study, Rat, 79-4980
 Glioma
 Transplantation, Heterologous, 79-4979
 Glycerophosphate Dehydrogenase
 Trigeminal Nerve, Rat, 79-5071
 Glycogenesis
 Liver, Mouse, 79-4981
 Hepatoma
 Transplacental Carcinogenesis, 79-4981
 Lung Neoplasms
 Adenoma, 79-4982
 Transplacental Carcinogenesis, 79-4982
 Lymphoma
 Transplacental Carcinogenesis, 79-4982
 Myelin Sheath
 Brain, Rat, 79-5071
- Urea, Methyl Nitroso-**
 Bladder Neoplasms
 Carcinoma, 79-4864
 Caffeine
 DNA Replication, 79-5057
 Hepatoma
 DNA Replication, 79-5057
 Microsomes, Liver
 DNA Replication, 79-5057
 Pancreatic Neoplasms
 Carcinogenic Potential, 79-5373
 Urea, Hydroxy-
 DNA Replication, 79-5057
- Urea, 1-(1-Naphthyl)-2-thio- (cont'd)**
 Ames Test
 Mutagenic Metabolite, 79-4984
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Ames Test, 79-4984
 Cell Transformation, Neoplastic
 Embryo, Hamster, 79-4984
- Urethral Neoplasms**
 Polyps
 Case Report, Child, 79-5342
- Uridine, 5-Bromo-2'-deoxy-**
 Chromatids
 Fish, 79-4998
 Radiation, Ionizing
 Chromosome Aberrations, 79-5101
 Virus, C-Type RNA Tumor
 Chromosomal Proteins, Non-Histone, 79-5225
 DNA, 79-5225
- Uridine, 2'-Deoxy-5-iodo-**
 Melanoma
 Virus Activation, 79-5231
 Virus, Murine Leukemia
 Ethidium Bromide, 79-5128
- Urinary Diversion**
 Colonic Neoplasms
 Adenocarcinoma, 79-5338
 Carcinoma, Colloid, 79-5338
- Urine**
 Acetamide, *N*-Fluoren-2-yl-
 Mutagenic Metabolite, 79-4963
 Antineoplastic Agents
 Mutagenic Metabolite, 79-5090
 Bladder Neoplasms
 Benzoic Acid, 2-Amino-3-oxy-, 79-5253
 Hydantoin, 1-((5-Nitrofurfurylidene)amino)-
 Mutagenic Activity, 79-5009
- Urogenital Neoplasms**
 Adenocarcinoma
 Neoplasms, Multiple Primary, 79-5348
 Carcinoma, Transitional Cell
 Neoplasms, Multiple Primary, 79-5348
 Epidemiology
 Japan, 79-5381
 Neoplasms, Multiple Primary
 Hypersensitivity, Delayed, 79-5281
 Immune Response, 79-5281
 Lymphocyte Transformation, 79-5281
- Uterine Neoplasms**
 Acanthosis Nigricans
 Case Report, 79-5349
 Adenocarcinoma
 Acanthosis Nigricans, 79-5349
 Benz(a)anthracene, 7,12-Dimethyl-, 79-5051
 Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 79-4978
 Phosphoric Acid, Trimethyl Ester, 79-4816
 Benz(a)anthracene, 7,12-Dimethyl-
 Ovariectomy, Hypophysectomy, 79-5051
 Precancerous Conditions, 79-5051
 Carcinoma
 Diabetes Mellitus, 79-5383
 Epidemiology, 79-5383
 Isoantigens, 79-5243
 Obesity, 79-5383

Uterine Neoplasms (cont'd)

- Carcinoma, Epidermoid
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5051
- Choriocarcinoma
 - Hydatidiform Mole, 79-5350
- Diabetes Mellitus
 - Epidemiology, Review, 79-4933
- Epidemiology
 - Rat, 79-5400
- Estrogenic Substances, Conjugated
 - Epidemiology, 79-5362
- Estrogens
 - Drug Therapy, 79-5089
 - Epidemiology, 79-5383
 - Epidemiology, Review, 79-4852, 79-4932
 - Risk Factors, Review, 79-4851
- Estrone
 - Epidemiology, 79-5383
- Ethane, 1,2-Dichloro-
 - Carcinogenic Activity, Mouse, Rat, 79-4961
- Hydatidiform Mole
 - Karyotyping, 79-5350
- Hypertension
 - Epidemiology, Review, 79-4933
- Isoantigens
 - Isolation and Characterization, 79-5243
- Obesity
 - Epidemiology, Review, 79-4933
- Phosphoric Acid, Trimethyl Ester
 - Carcinogenic Activity, Mouse, Rat, 79-4816
- Polyps
 - Precancerous Conditions, Review, 79-4933
- Pregn-4-ene-3,20-dione, 17-(Acetyloxy)-6 α -methyl-
 - Epidemiology, 79-5354
- Premarin
 - Epidemiology, 79-5354
- Progestational Hormones
 - Drug Therapy, 79-5089

Uterus

- Estradiol
 - Receptors, Estrogen, 79-5087

Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester, HCl

- Diethylamine, *N*-Nitroso-
 - Nucleic Acids, 79-4990

Valine, 3-Mercapto-

- Bone Marrow Diseases
 - Toxicity, Review, 79-4834
- Lupus Erythematosus
 - Neoplasms, 79-4834

Vinblastine

- Neuroblastoma
 - Isolation and Characterization, 79-5394

Vinblastine Sulfate

- Chromatids
 - Chromosome Aberrations, 79-4994

Viral Interference

- Virus, SV40
 - Defective-Particle Mutants, 79-5221
 - Kidney Cells, Monkey, 79-5221
 - Viral Proteins, 79-5221

Viral Proteins

- Plasmacytoma
 - Cell Differentiation, 79-5264
- Virus, Adeno

Viral Proteins (cont'd)

- Subgroup Classification, 79-5197
- Virus, Hamster C-Type RNA Tumor
 - Reverse Transcriptase, 79-5147
- Virus, Herpes
 - Cell Membrane, Review, 79-4869
- Virus, Kirsten Murine Sarcoma
 - Pseudotype Virus, 79-5141
- Virus, Polyoma
 - Lysosomes, 79-5206
 - RNA, Messenger, 79-5204
- Virus, Rauscher Murine Leukemia
 - Chromosomes, 79-5135
 - DNA, Binding, 79-5135
- Virus, SV40
 - RNA, Messenger, 79-5211
 - Viral Interference, 79-5221
- Virus, Vesicular Stomatitis
 - Ultraviolet Rays, 79-5230
- Virus, Woolly Monkey
 - Pseudotype Virus, 79-5141

Viral Vaccines

- Small Pox
 - Immunization, Review, 79-4897
- Virus, Marek's Disease Herpes
 - Virus, Turkey Herpes, 79-5125

Virus, Abelson Murine Leukemia

- Virus, Murine Hepatitis
 - Cytopathogenic Effect, Viral, 79-5142

Virus Activation

- Astrocytoma
 - Virus, Adeno 5, 79-5200
- Glioblastoma Multiforme
 - Virus, Adeno 5, 79-5200
- Melanoma
 - Uridine, 2'-Deoxy-5-iodo-, 79-5231
 - Virus, Murine Leukemia, 79-5231
- Neoplasms
 - Virus, Adeno 5, 79-5200
- Virus, C-Type RNA Tumor
 - Millardia melitana*, 79-5140
- Virus, Cytomegalo
 - Antilymphocyte Serum, 79-5158
 - Cortisone Acetate, 79-5158

Virus, Adeno

- RNA, Messenger
 - Virus Serotype, 79-5202
- Viral Proteins
 - Subgroup Classification, 79-5197

Virus, Adeno 2

- DNA Replication
 - Temperature Sensitive Mutants, 79-5198
- DNA, Viral
 - DNA Replication, 79-5198
- Virus, SV40
 - Virus, Helper, 79-5215

Virus, Adeno 3

- RNA, Messenger
 - DNA-RNA Hybridization, 79-5202
 - Nucleotide Sequence, 79-5202

Virus, Adeno 5

- Astrocytoma
 - Virus Activation, 79-5200
- Brain Neoplasms

- Virus, Adeno 5 (cont'd)**
 DNA Repair, 79-5200
 Glioblastoma Multiforme
 Virus Activation, 79-5200
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 DNA Repair, 79-5200
 Neoplasms
 Virus Activation, 79-5200
- Virus, Adeno 7**
 RNA, Messenger
 DNA-RNA Hybridization, 79-5202
 Nucleotide Sequence, 79-5202
- Virus, Adeno 12**
 α -Amanitine
 RNA Replication, 79-5201
 RNA, Viral
 Nucleotide Sequence, 79-5201
 Virus Replication, 79-5201
- Virus, Adeno 2 - SV40 Hybrid**
 Antigens, Neoplasm
 RNA, Messenger, 79-5199
 Virus, SV40
 DNA-RNA Hybridization, 79-5199
 RNA, Viral, 79-5199
- Virus, Avian Leukosis-Sarcoma**
 Virus, Marek's Disease Herpes
 Virus Replication, 79-5124
 Virus, Rous-Associated
 Antigenic Determinants, 79-5118
- Virus, Avian Reticuloendotheliosis**
 Bone Marrow
 Cell Transformation, Neoplastic, 79-5120
 Fibroblasts
 Cell Transformation, Neoplastic, 79-5120
- Virus, Bovine Papilloma**
 DNA, Viral
 Nucleic Acid Hybridization, 79-5156
 Fibroma
 DNA, Viral, 79-5156
 Soft Tissue Neoplasms
 DNA, Viral, 79-5156
- Virus, Bovine Parvo**
 α -Amanitine
 RNA Replication, 79-5155
 RNA Polymerase
 RNA Replication, 79-5155
- Virus, C-Type RNA Tumor**
 DNA
 Nucleoproteins, 79-5225
Millardia meltada
 Virus Activation, 79-5140
 Uridine, 5-Bromo-2'-deoxy-
 Chromosomal Proteins, Non-Histone, 79-5225
 DNA, 79-5225
 Virus, Herpes
 Co-carcinogenic Effect, Review, 79-4880
 Virus Activation, Review, 79-4880
- Virus Cultivation**
 Melanoma
 Virus, Murine Sarcoma, 79-5231
 Virus, Epstein-Barr
 Leukocytes, 79-5162
 Radiation, Ionizing, 79-5162
- Virus, Cytomegalo**
 Antilymphocyte Serum
 Virus Activation, 79-5158
 Carcinogenic Potential
 Review, 79-4886
 Cell Transformation, Neoplastic
 Review, 79-4872
 Cervix Neoplasms
 Antibodies, Viral, 79-5175
 Cortisone Acetate
 Virus Activation, 79-5158
 Virus Replication, 79-5158
 Immunosuppression
 Virus Replication, 79-5158
 Pregnancy
 Antibodies, Viral, 79-5175
 Virus, Epstein-Barr
 DNA Replication, Review, 79-4868
- Virus, D-Type RNA Tumor**
 Breast Neoplasms
 Antigens, Viral, 79-5226
- Virus, Epstein-Barr**
 Antigen-Antibody Complex
 Immune Response, Review, 79-4890
 Antigenic Determinants
 Primate Viruses, Review, 79-4879
 Antigens, Viral
 Latent Infections, Review, 79-4878
 Lymphocyte Transformation, 79-5161
 B-Lymphocytes, 79-5171
 Burkitt's Lymphoma
 Antibodies, Viral, 79-5166, 79-5167
 Antigen-Antibody Complex, 79-5165
 Epidemiology, Review, 79-4894
 Hypersensitivity, Delayed, 79-5167
 Molecular Biology, Review, 79-4896
 Carcinogenic Potential
 Review, 79-4886, 79-4892
 Cell Transformation, Neoplastic
 Nonlymphoid Cells, Review, 79-4870
 Review, 79-4872
 Complement 3
 Lymphocyte Transformation, Review, 79-4890
 B-Lymphocytes, 79-5171
 Cycloheximide
 B-Lymphocytes, 79-5161
 Cytosine, 1- β -D-Arabinofuranosyl-
 B-Lymphocytes, 79-5161
 DNA, Circular
 Nucleic Acid Renaturation, 79-5160
 DNA, Viral
 Cell Transformation, Neoplastic, Review, 79-4871
 79-4889
 Centrifugation, Review, 79-4893
 Endonucleases, 79-5160
 Epithelial Cells, 79-5169
 Epithelial Cells, Lymphocytes, Review, 79-4896
 Integration, Review, 79-4893
 Plasmids, Review, 79-4867
 Strain Difference, Review, 79-4889
 Epithelial Cells
 Virus Replication, Review, 79-4878
 Extrachromosomal Inheritance
 Virus Replication, Review, 79-4896
 Glycoproteins
 Cell Membrane, 79-5164

irus, Epstein-Barr (cont'd)

- Head and Neck Neoplasms
 - Antibodies, Viral, 79-5166
- Hematopoietic Stem Cells
 - Glycoproteins, 79-5164
- Hodgkin's Disease
 - Antigens, Viral, 79-5171
- Hypersensitivity, Delayed
 - Antibodies, Viral, 79-5167
- Infectious Mononucleosis
 - Antibodies, Viral, 79-5166
 - Antigens, Viral, 79-5171
 - DNA-RNA Hybridization, 79-5169
 - Epidemiology, Review, 79-4894
 - Epithelial Cells, 79-5169
 - Immune Response, Review, 79-4895
 - Immunity, Cellular, 79-5170
 - Leukocytes, 79-5168
 - Lymphocyte Transformation, Review, 79-4895
 - Molecular Biology, Review, 79-4896
 - Saliva, 79-5166
- Leukocytes
 - Virus Cultivation, 79-5162
 - Virus Replication, 79-5168
- Lymphocyte Transformation
 - Fetal Blood, 79-5162
 - Virus Rescue, 79-5162
- B-Lymphocytes
 - DNA Replication, 79-5161
 - Fetal Blood, 79-5161
 - Killer Cells, Review, 79-4890
 - Lymphocyte Transformation, 79-5161
 - Lymphocyte Transformation, Review, 79-4890
 - 79-4891, 79-4894
 - Virus Replication, Review, 79-4878
- Lymphoma
 - Antigens, Viral, 79-5171
- Malaria
 - Immunity, Cellular, Review, 79-4882
- Nasopharyngeal Neoplasms
 - Antibodies, Viral, 79-5166, 79-5167
 - Carcinogenic Potential, Review, 79-4888
 - Epidemiology, Review, 79-4894
 - IgA, 79-5166
 - Molecular Biology, Review, 79-4896
 - Saliva, 79-5166
 - Seroepidemiology, Review, 79-4873
- Phosphonoacetic Acid
 - Lymphocyte Transformation, 79-5168
 - Virus Replication, 79-5168
- Plant Agglutinins
 - Lymphocyte Transformation, 79-5170
- Radiation, Ionizing
 - Virus Cultivation, 79-5162
- Radioactive Fallout
 - Chromosome Aberrations, 79-5096, 79-5097
- RNA, Messenger
 - DNA Replication, Review, 79-4868
- Tonsillitis
 - Antigens, Viral, 79-5171
- Virus, Cytomegalo
 - DNA Replication, Review, 79-4868
- Virus, Herpes Simplex
 - Virus Replication, 79-5174

Virus, Feline Leukemia

- Antigenic Determinants
 - Antigen-Antibody Reactions, 79-5152

Virus, Feline Leukemia (cont'd)

- Virus, Feline Sarcoma
 - Antigenic Determinants, 79-5152

Virus, Feline Sarcoma

- Antigenic Determinants
 - Antigen-Antibody Reactions, 79-5152
- RNA, Viral
 - DNA-RNA Hybridization, 79-5151
 - Nucleotide Sequence, 79-5151
- Virus, Feline Leukemia
 - Antigenic Determinants, 79-5152

Virus, Friend Murine Leukemia

- Erythroleukemia
 - DNA-RNA Hybridization, 79-5130
 - Methanesulfonic Acid, Methyl Ester, 79-4952
- Methanesulfonic Acid, Methyl Ester
 - Antibody Formation, 79-4952
 - Co-carcinogenic Effect, 79-4952
- RNA, Viral
 - DNA-RNA Hybridization, 79-5130
 - Virus, Friend Spleen Focus-Forming, 79-5130

Virus, Friend Spleen Focus-Forming

- Glycoproteins
 - Antigenic Determinants, 79-5131
- RNA, Viral
 - Virus, Helper, 79-5130
- Virus, Friend Murine Leukemia
 - RNA, Viral, 79-5130
- Virus, Mink Cell Focus-Inducing
 - Antigenic Determinants, 79-5131

Virus, Gazdar Murine Sarcoma

- Antigenic Determinants
 - Radioimmunoassay, 79-5139
- Virus, Helper
 - Antigenic Determinants, 79-5139

Virus, Gross Murine Sarcoma

- Virus, Helper
 - Antigenic Determinants, 79-5139

Virus, Guinea Pig Herpes

- Cell Transformation, Neoplastic
 - Nonlymphoid Cells, Review, 79-4870
- Leukemia
 - Viral Interactions, 79-5149
- Lymphoid Tissue
 - Leukemia, 79-5149
- Virus, Guinea Pig RNA Tumor
 - Viral Interactions, 79-5149

Virus, Guinea Pig RNA Tumor

- Hyperplasia
 - Viral Interactions, 79-5149
- Leukemia
 - Viral Interactions, 79-5149
- Lymphoid Tissue
 - Leukemia, 79-5149
- Virus, Guinea Pig Herpes
 - Viral Interactions, 79-5149

Virus, Hamster C-Type RNA Tumor

- Melanoma
 - Isolation and Characterization, 79-5148
- Peptides
 - Antigenic Determinants, 79-5148
- Reverse Transcriptase
 - Isolation and Characterization, 79-5147

Virus, Hamster C-Type RNA Tumor (cont'd)

- Viral Proteins, 79-5147
- RNA, Viral
- Reverse Transcriptase, 79-5148

Virus, Harvey Murine Sarcoma

- Cell Differentiation
- Bone Marrow, Adipocytes, 79-5144
- Cortisol Acetate
- Cell Differentiation, 79-5144
- Insulin
- Cell Differentiation, 79-5144

Virus, Helper

- Virus, Adeno 2
- Virus, SV40, 79-5215
- Virus, Friend Spleen Focus-Forming
- RNA, Viral, 79-5130
- Virus, Gazdar Murine Sarcoma
- Antigenic Determinants, 79-5139
- Virus, Gross Murine Sarcoma
- Antigenic Determinants, 79-5139
- Virus, Kirsten Murine Sarcoma
- Cell Transformation, Neoplastic, 79-5141
- Virus, Woolly Monkey, 79-5141
- Virus, Moloney Murine Sarcoma
- Antigenic Determinants, 79-5139
- Virus, Polyoma
- Host Range Mutants, 79-5207
- Virus, SV40
- Antigens, Neoplasm, 79-5215
- Deletion Mutants, 79-5215

Virus, Hepatitis B

- Hepatoma
- Epidemiology, Review, 79-4898

Virus, Herpes

- Adenocarcinoma
- Cells, Cultured, Review, 79-4870
- Antibody Formation
- Immune Response, Review, 79-4875
- Antigen-Antibody Reactions
- Immune Response, Review, 79-4877
- Antigenic Determinants
- Isolation and Characterization, Review, 79-4876
- Cell Transformation, Neoplastic
- Nonlymphoid Cells, Review, 79-4870
- Review, 79-4872
- DNA Repair
- Co-carcinogenic Effect, Review, 79-4880
- DNA Replication
- Virus, Recombinant, Review, 79-4867
- DNA, Viral
- Isolation and Characterization, Review, 79-4875
- Nucleic Acid Homology, Review, 79-4879
- Fibrosarcoma
- Cells, Cultured, Review, 79-4870
- Glycoproteins
- Cell Fusion, Review, 79-4876
- Cell Membrane, Review, 79-4869
- Horizontal Transmission
- Fish, Review, 79-4881
- Immune Response
- Animal Model, Mouse, Review, 79-4874
- Leukocytes
- Virus Replication, Review, 79-4877
- B-Lymphocytes
- Carcinogenic Activity, Review, 79-4883

Virus, Herpes (cont'd)

- Lymphocyte Transformation, Review, 79-4879
- 79-4891
- T-Lymphocytes
- Carcinogenic Activity, Review, 79-4883
- Immunity, Cellular, Review, 79-4874
- Lymphoma
- Immune Response, Review, 79-4875
- Pulmonary Adenomatosis, Ovine
- Co-carcinogenic Effect, 79-5153
- DNA-RNA Hybridization, 79-5153
- Horizontal Transmission, 79-5153
- Receptors, Fc
- Cell Membrane, Review, 79-4877
- Skin Neoplasms
- Fish, Review, 79-4881
- Hyperplasia, 79-4881
- Ultraviolet Rays
- Virus Activation, Review, 79-4880
- Viral Proteins
- Cell Membrane, Review, 79-4869
- Virus, C-Type RNA Tumor
- Co-carcinogenic Effect, Review, 79-4880
- Virus Activation, Review, 79-4880
- Virus, Herpes Ateles
- Carcinogenic Activity, Review, 79-4883

Virus, Herpes Ateles

- Genetics
- Immunity, Cellular, Review, 79-4882
- Host Range
- Carcinogenic Activity, Review, 79-4883
- Virus, Herpes
- Carcinogenic Activity, Review, 79-4883

Virus, Herpes Lucke

- Antigens, Viral
- Latent Infections, Review, 79-4878
- Epithelial Cells
- Virus Replication, Review, 79-4878
- IgG
- Antibody Formation, 79-5126
- Cell Differentiation, 79-5126
- Kidney Neoplasms
- Perinatal Exposure, 79-5126
- Seroepidemiology, Review, 79-4873
- Stress
- Immunity, Cellular, Review, 79-4882

Virus, Herpes Papio

- B-Lymphocytes
- Lymphocyte Transformation, Review, 79-4891

Virus, Herpes Saimiri

- Genetics
- Immunity, Cellular, Review, 79-4882
- Host Range
- Carcinogenic Activity, Review, 79-4883

Virus, Herpes Simplex

- Carcinogenic Potential
- Review, 79-4886
- Cervix Neoplasms
- Antibodies, Viral, 79-5175
- Carcinogenic Potential, Review, 79-4882
- DNA, Viral
- Cell Transformation, Neoplastic, Review, 79-4871
- Thymidine Kinase, 79-4871
- Virus, Recombinant, Review, 79-4868
- Gastrointestinal Neoplasms

Virus, Herpes Simplex (cont'd)

- Antigen-Antibody Reactions, 79-5191
 - Hodgkin's Disease
 - Antigen-Antibody Reactions, 79-5191
 - Leukemia, Myelocytic
 - Antigen-Antibody Reactions, 79-5191
 - Lung Neoplasms
 - Antigen-Antibody Reactions, 79-5191
 - B-Lymphocytes
 - Virus Replication, 79-5174
 - T-Lymphocytes
 - Virus Replication, 79-5174
 - Mitogens
 - T-Lymphocytes, 79-5174
 - Neurons
 - Virus Replication, Review, 79-4878
 - Peptides
 - Cell-Free Translation System, 79-4884
 - Pregnancy
 - Antibodies, Viral, 79-5175
 - Prostatic Neoplasms
 - Antigen-Antibody Reactions, 79-5191
 - RNA, Messenger
 - Cell-Free Translation System, 79-4884
 - DNA Replication, Review, 79-4868
 - Virus, Epstein-Barr
 - Virus Replication, 79-5174
- ## **Virus, Herpes Simplex 1**
- Adenocarcinoma
 - Histocompatibility Antigens, 79-5184
 - Neoplasm Metastasis, 79-5184
 - Amino Acids
 - Peptide Chain Elongation, 79-5178
 - Anti-Antibodies
 - IgG, 79-5183
 - Pyruvate Kinase, 79-5183
 - Antigens, Viral
 - HEP-2-Cells, Isolation and Characterization 79-5190
 - Carcinoma, Epidermoid
 - Seroepidemiology, Review, 79-4873
 - Cell Membrane Permeability
 - Chromium Release Assay, 79-5185
 - Complement
 - Hemolysins, 79-5185
 - Deoxyribonuclease
 - Antibody Specificity, 79-5191
 - DNA, Viral
 - Nucleotide Sequence, 79-5188, 79-5189
 - Peptides, 79-5189
 - RNA, Messenger, 79-5177
 - Virus, Recombinant, 79-5189
 - Endonucleases
 - DNA-RNA Hybridization, 79-5177
 - Genetics
 - Immune Response, Mouse, 79-5182
 - Graft Rejection
 - Immune Response, Mouse, 79-5182
 - Hepatitis
 - Cytopathogenic Effects, *Tupaia*, 79-5192
 - Histocompatibility Antigens
 - Neoplasm Metastasis, 79-5184
 - Transplantation Immunology, 79-5184
 - IgA, Secretory
 - Virus Replication, 79-5241
 - Immune Serums
 - Cell Membrane Permeability, 79-5185

Virus, Herpes Simplex 1 (cont'd)

- Lactate Dehydrogenase, 79-5183
- Proteins, 79-5183
- Immunization
 - Neoplasm Metastasis, 79-5184
- Interferon
 - Anti-Antibodies, 79-5173
 - Immune Response, Mouse, 79-5173
 - Virus Replication, 79-5241
- Lipopolysaccharides
 - Immune Response, Mouse, 79-4911
 - Virus Replication, 79-4911
- Lymphocyte Transformation
 - Immunity, Cellular, 79-5181
- T-Lymphocytes
 - Immunosuppression, 79-5182
- Lymphoma
 - Trigeminal Nerve, 79-5186
- Macrophages
 - Cell Migration Inhibition, 79-5181
 - Immunity, Cellular, 79-5181
 - Immunosuppression, 79-5182
- Mitogens
 - Cell Supernatant, 79-5187
 - DNA Replication, 79-5187
- Multiple Sclerosis
 - Trigeminal Nerve, 79-5186
- Neuroblastoma
 - Virus Replication, 79-5241
- Nucleic Acids
 - Virus Replication, Review, 79-4885
- Nucleotide Sequence
 - Temperature Sensitive Mutants, 79-5188
- Peptides
 - Genes, Viral, 79-5188
 - Virus Replication, Review, 79-4885
- Phosphonoacetic Acid
 - Genes, Viral, 79-5179
- Plant Agglutinins
 - Lymphocyte Transformation, 79-5181
- Poly ADP Ribose Polymerase
 - Chromatin, 79-5176
 - DNA Replication, 79-5176
- Proteins
 - Polyribosomes, 79-5178
- Radiation, Ionizing
 - Immunosuppression, 79-5182
- Thymidine Kinase
 - Antibody Specificity, 79-5191
 - Cell Transformation, Neoplastic, 79-5180
 - Enzymatic Activity, 79-5180
 - Genes, Viral, 79-5179, 79-5180
 - Nucleotide Sequence, 79-5188
- Trigeminal Nerve
 - Virus Isolation, 79-5186
- Triton X 100
 - Cell Membrane Permeability, 79-5185
- Tuberculin
 - Lymphocyte Transformation, 79-5181
- Virus, Herpes Simplex 2
 - Virus, Recombinant, 79-5188, 79-5189
- Virus, Recombinant
 - Genotype, 79-5179
- Virus Replication
 - Ganglia, Rabbit, 79-5241
 - Lymphocytes, 79-5192
 - Nervous System, 79-5192

Virus, Herpes Simplex 2

Antibodies

Hypersensitivity, Delayed, 79-5194

Antigens, Viral

HEP-2-Cells, Isolation and Characterization
79-5190

Carcinogenic Potential

Review, 79-4892

Cervix Neoplasms

Carcinoma In Situ, 79-5193

DNA-RNA Hybridization, 79-5193

Precancerous Conditions, 79-5193

RNA, Messenger, 79-5193

Seroepidemiology, Review, 79-4873

Cholanthrene, 3-Methyl-

Co-carcinogenic Effect, 79-5196

Deoxyribonuclease

Antibody Specificity, 79-5191

DNA, Viral

Nucleotide Sequence, 79-5189

Peptides, 79-5189

Virus, Recombinant, 79-5189

Fibrosarcoma

Neoplasm Transplantation, 79-5236

Temperature Sensitive Mutants, 79-5236

Hepatitis

Cytopathogenic Effects, *Tupaia*, 79-5192

Immunity, Cellular

Systemic, Vaginal Infections, 79-5194

Immunosuppression

Neoplasm Transplantation, 79-5236

Leukocytes

Adult, Infant, 79-5195

Virus Replication, 79-5195

T-Lymphocytes

Immunity, Cellular, 79-5194

Macrophages

Immunity, Cellular, 79-5194

Mitogens

Cell Supernatant, 79-5187

DNA Replication, 79-5187

Neoplasms, Experimental

Cholanthrene, 3-Methyl-, 79-5196

Neuroblastoma

Virus Replication, 79-5241

Nucleic Acids

Virus Replication, Review, 79-4885

Peptides

Virus Replication, Review, 79-4885

Radiation, Ionizing

Neoplasm Transplantation, 79-5236

Thymidine Kinase

Antibody Specificity, 79-5191

Virus, Herpes Simplex 1

Virus, Recombinant, 79-5188, 79-5189

Virus Replication

Lymphocytes, 79-5192

Nervous System, 79-5192

Virus, Kilham Rat

DNA, Single Stranded

Nucleotide Sequence, 79-5146

Virus, Kirsten Murine Leukemia

Ethidium Bromide

Virus, Kirsten Murine Sarcoma, 79-5128

Millardia meltda

Cell Transformation, Neoplastic, 79-5140

Virus, Kirsten Murine Sarcoma

Cell Differentiation

Bone Marrow, Adipocytes, 79-5144

Cortisol Acetate

Cell Differentiation, 79-5144

Cytosine, 2,2'-Anhydro-1- β -D-arabinofuranosyl-

Virus Replication, 79-5143

Cytosine, 1- β -D-Arabinofuranosyl-

Virus Replication, 79-5143

Ethidium Bromide

Cell Survival, 79-5128

Insulin

Cell Differentiation, 79-5144

s-Triazin-2(1H)-one, 4-Amino-1- β -D-ribofuranosyl-

Virus Replication, 79-5143

Viral Proteins

Pseudotype Virus, 79-5141

Virus, Helper

Cell Transformation, Neoplastic, 79-5141

Virus, Kirsten Murine Leukemia^a

Ethidium Bromide, 79-5128

Virus, Murine Hepatitis

Cytopathogenic Effect, Viral, 79-5142

Virus, Woolly Monkey

Virus, Helper, 79-5141

Virus-Like Particles

Keratoacanthoma

Ultrastructural Study, 79-5222

Virus, Marek's Disease Herpes

Antigens

Immunity, Cellular, 79-5122

Antigens, Viral

B-Lymphocytes, 79-5124

T-Lymphocytes, 79-5124

Avian Leukosis

B-Lymphocytes, 79-5124

Corynebacterium parvum

Hypersensitivity, Delayed, 79-5125

Freund's Adjuvant

Transplantation Immunology, 79-5122

Genetics

Immunity, Cellular, Review, 79-4882

Glutaraldehyde

Transplantation Immunology, 79-5122

Histocompatibility Antigens

Genetic Resistance, 79-5121

Transplantation Immunology, 79-5121

T-Lymphocytes

Immune Response, Review, 79-4890

Lymphocyte Depletion, 79-5123

Lymphocyte Transformation, Review, 79-4890

Mitogens, 79-5123

Lymphoma

Histocompatibility Antigens, 79-5121

Immunity, Cellular, 79-5122

T-Lymphocytes, 79-5124

Tumor-Cell Vaccines

Immunization, 79-5125

Virus, Avian Leukosis-Sarcoma

Virus Replication, 79-5124

Virus, Turkey Herpes

Immunity, Cellular, 79-5125

Viral Vaccines, 79-5125

Virus, Mason-Pfizer Monkey

Cell Fusion

Virus Replication, 79-5157

Virus, Mason-Pfizer Monkey (cont'd)

- Cycloheximide
 - Cell Fusion, 79-5157
- Cytosine, 1- β -D-Arabinofuranosyl-
 - Cell Fusion, 79-5157
- Ultraviolet Rays
 - Cell Fusion, 79-5157

Virus, Measles

- Antibodies, Viral
 - Cell Membrane, 79-5228
 - Hemolysins, 79-5228
 - Phosphoproteins, 79-5228

Virus, Mink Cell Focus-Inducing

- Glycoproteins
 - Antigenic Determinants, 79-5131
- Membrane Proteins
 - Antigenic Determinants, 79-5145
- Virus, Friend Spleen Focus-Forming
 - Antigenic Determinants, 79-5131
- Virus, Murine Leukemia
 - Antigenic Determinants, 79-5145

Virus, Moloney Murine Leukemia

- Asbestos
 - Co-carcinogenic Effect, 79-4943
- Carbon
 - Co-carcinogenic Effect, 79-4943
- DNA, Viral
 - Endonucleases, 79-5133
 - Fibroblasts, Integration Sites, 79-5133
- Magnesium
 - DNA Replication, 79-5132
- Manganese
 - DNA Replication, 79-5132
- Nucleotides
 - DNA Replication, 79-5132
- Quartz
 - Co-carcinogenic Effect, 79-4943
- Reverse Transcriptase
 - Cations, Divalent, 79-5132
- Sarcoma
 - Asbestos, 79-4943
- Virus, Polyoma
 - Virus Replication, 79-5207

Virus, Moloney Murine Sarcoma

- Cell Differentiation
 - Bone Marrow, Adipocytes, 79-5144
- Cortisol Acetate
 - Bone Marrow, Adipocytes, 79-5144
- Insulin
 - Cell Differentiation, 79-5144
- Temperature Sensitive Mutants
 - Isolation and Characterization, 79-5134
- Ultraviolet Rays
 - Temperature Sensitive Mutants, 79-5134
- Virus, Helper
 - Antigenic Determinants, 79-5139
- Virus, Murine Leukemia
 - Virus Rescue, 79-5134

Virus, Murine Hepatitis

- Virus, Abelson Murine Leukemia
 - Cytopathogenic Effect, Viral, 79-5142
- Virus, Kirsten Murine Sarcoma
 - Cytopathogenic Effect, Viral, 79-5142

Virus, Murine Leukemia

- Ethidium Bromide
 - Uridine, 2'-Deoxy-5-iodo-, 79-5128
- Virus, Replication, 79-5128
- Genetics
 - Virus Replication, 79-5127
 - X-Tropic NZB Virus, 79-5127
- Melanoma
 - Virus Activation, 79-5231
- Membrane Proteins
 - Antigenic Determinants, 79-5145
- Virus, Mink Cell Focus-Inducing
 - Antigenic Determinants, 79-5145
- Virus, Moloney Murine Sarcoma
 - Virus Rescue, 79-5134

Virus, Murine Mammary Tumor

- Mammary Neoplasms, Experimental
 - Neoplasm Metastasis, 79-5344

Virus, Murine Sarcoma

- Melanoma
 - Virus Cultivation, 79-5231
- Millardia meltda*
 - Cell Transformation, Neoplastic, 79-5140

Virus, Murine Sarcoma-Leukemia

- Interferon
 - Cell Transformation, Neoplastic, 79-5129
 - Clone Cells, 79-5129

Virus, Papilloma

- Carcinogenic Potential
 - Review, 79-4892
- Epidermodysplasia Verruciformis
 - Antibodies, Viral, 79-5172
 - Genetics, 79-5172
 - Immunity, Cellular, 79-5172

Virus, Papova

- Cells, Cultured
 - Carcinogenic Potential, Review, 79-4888

Virus, Polyoma

- DNA Replication
 - Cell Nucleus, 79-5203
- DNA, Viral
 - Bacteriophages, 79-5208
 - Cell Transformation, Neoplastic, 79-5205
 - Extrachromosomal Inheritance, 79-5208
- Endonucleases
 - DNA Replication, 79-5203
- Fibroblasts
 - Transformation, Genetic, 79-5208
- Genes, Viral
 - Host Range Mutants, 79-5207
- Lysosomes
 - DNA, Viral, 79-5206
 - Viral Proteins, 79-5206
- RNA, Messenger
 - DNA Replication, 79-5204
 - Nucleotide Sequence, 79-5204
 - Viral Proteins, 79-5204
- Virus, Helper
 - Host Range Mutants, 79-5207
- Virus, Moloney Murine Leukemia
 - Virus Replication, 79-5207
- Virus Replication
 - Cell Transformation, Neoplastic, 79-5205
- Virus, Sendai

- Virus, Polyoma (cont'd)**
Cell Membrane Permeability, 79-5206
- Virus, Pox**
Hypersensitivity
Immunization, Review, 79-4897
Myxomatosis, Infectious
Animal Pest Control, Review, 79-4897
Virus, Recombinant
Isolation and Characterization, Review, 79-4897
- Virus, Rauscher Murine Leukemia**
DNA Polymerase
Enhancing Factor, Egg Fluids, 79-5136
DNA Replication
Carcinogenic Activity, 79-5136
Glycoproteins
Cell Transformation, Neoplastic, 79-5137
Lymphoid Tissue, Binding, 79-5137
Reverse Transcriptase
Attenuated Virus, 79-5138
RNA, Viral
Attenuated Virus, 79-5138
Viral Proteins
Chromosomes, 79-5135
DNA, Binding, 79-5135
Virus Replication
Enhancing Factor, Egg Fluids, 79-5136
- Virus, Recombinant**
Virus, Herpes Simplex 1
DNA, Viral, 79-5189
Genotype, 79-5179
Virus, Herpes Simplex 2, 79-5188, 79-5189
Virus, Herpes Simplex 2
DNA, Viral, 79-5189
Virus, Pox
Isolation and Characterization, Review, 79-4897
Virus, Rous Sarcoma
Genes, Viral, 79-5117
- Virus Replication**
Infectious Mononucleosis
Phosphonoacetic Acid, 79-5168
Neuroblastoma
Virus, Herpes Simplex 1, 79-5241
Virus, Herpes Simplex 2, 79-5241
Virus, Adeno 12
RNA, Viral, 79-5201
Virus, Cytomegalo
Cortisone Acetate, 79-5158
Immunosuppression, 79-5158
Virus, Epstein-Barr
Leukocytes, 79-5168
Phosphonoacetic Acid, 79-5168
Virus, Herpes Simplex
B-Lymphocytes, 79-5174
T-Lymphocytes, 79-5174
Virus, Epstein-Barr, 79-5174
Virus, Herpes Simplex 1
Ganglia, Rabbit, 79-5241
IgA, Secretory, 79-5241
Interferon, 79-5241
Lipopolysaccharides, 79-4911
Lymphocytes, 79-5192
Nervous System, 79-5192
Virus, Herpes Simplex 2
Leukocytes, 79-5195
Lymphocytes, 79-5192
- Virus Replication (cont'd)**
Nervous System, 79-5192
Virus, Kirsten Murine Sarcoma
Cytosine, 2,2'-Anhydro-1- β -D-arabinofuranosyl-
79-5143
Cytosine, 1- β -D-Arabinofuranosyl-, 79-5143
s-Triazin-2(1H)-one, 4-Amino-1- β -D-ribofuranosyl-
79-5143
Virus, Marek's Disease Herpes
Virus, Avian Leukosis-Sarcoma, 79-5124
Virus, Mason-Pfizer Monkey
Cell Fusion, 79-5157
Virus, Murine Leukemia
Ethidium Bromide, 79-5128
Genetics, 79-5127
Virus, Polyoma
Cell Transformation, Neoplastic, 79-5205
Virus, Moloney Murine Leukemia, 79-5207
Virus, Rauscher Murine Leukemia
Enhancing Factor, Egg Fluids, 79-5136
Virus, SV40
DNA, Viral, 79-5209
Mitomycin C, 79-5209
Radiation, Ionizing, 79-5209
Virus, Visna
Phosphonoacetic Acid, 79-5154
Phosphonoformic Acid, Trisodium Salt, 79-5154
- Virus, Reticuloendotheliosis**
Chromosomes
Cell Transformation, Neoplastic, 79-5119
DNA, Viral
Chromosomes, 79-5119
- Virus, RNA Tumor**
A-Type Particles
Embryo, Mouse, 79-5223
Breast Neoplasms
Carcinogenic Potential, Review, 79-4888
Leukemia, Myeloblastic
Transformation, Genetic, 79-5224
Lymphoma
Carcinogenic Potential, Review, 79-4888
- Virus, Rous-Associated**
Phenotype
Chick Embryo, 79-5118
Reverse Transcriptase
Phenotype, 79-5118
Virus, Avian Leukosis-Sarcoma
Antigenic Determinants, 79-5118
Virus, Rous Sarcoma
Antigenic Determinants, 79-5118
- Virus, Rous Sarcoma**
DNA, Viral
Nucleic Acid Synthesis, 79-5115
Transformation, Genetic, 79-5115
Glycoproteins
Antigenic Determinants, 79-5116
Fibroblasts, 79-5227
Potassium
Cell Transformation, Neoplastic, 79-5227
Sodium
Cell Transformation, Neoplastic, 79-5227
Succinate Dehydrogenase
Fibroblasts, 79-5227
Tunicamycin
Glycoproteins, 79-5116

- Virus, Rous Sarcoma (cont'd)**
 - Peptides, 79-5116
- Virus, Recombinant**
 - Genes, Viral, 79-5117
- Virus, Rous-Associated**
 - Antigenic Determinants, 79-5118
- Virus, Sendai**
 - Glycoproteins
 - Cell Membrane, 79-5229
 - Hemagglutination, 79-5229
 - Neuraminidase, 79-5229
 - Phosphatidylcholines
 - Cell Membrane, 79-5229
 - Triton X 100
 - Membrane Proteins, 79-5229
 - Virus, Polyoma
 - Cell Membrane Permeability, 79-5206
- Virus, Shope Rabbit Papilloma**
 - Carcinoma
 - DNA, Viral, 79-5150
 - Neoplasm Metastasis, 79-5150
 - DNA, Viral
 - Neoplasm Metastasis, 79-5150
 - Papilloma
 - DNA, Viral, 79-5150
- Virus, Sindbis**
 - Potassium
 - Protein Synthesis, 79-5227
 - RNA, Messenger
 - Protein Synthesis, 79-5227
 - Sodium
 - Protein Synthesis, 79-5227
- Virus, SV40**
 - Actin
 - Cell Adhesion, 79-5219
 - Antigens, Neoplasm
 - Cell Cycle Kinetics, 79-5216
 - Deletion Mutants, 79-5214
 - DNA Replication, 79-5216
 - Nucleotide Sequence, 79-5212, 79-5213
 - RNA, Messenger, 79-5214
 - Cell Adhesion
 - Cell Transformation, Neoplastic, 79-5219
 - Cell Membrane
 - Surface Charge, 79-5220
 - DNA Replication
 - Temperature Sensitive Mutants, 79-5216
 - DNA, Viral
 - Deletion Mutants, 79-5212, 79-5213, 79-5215
 - Nucleotide Sequence, 79-5212
 - Virus Replication, 79-5209
 - Formaldehyde
 - Cell Membrane, 79-5220
 - Glycoproteins
 - Cell Transformation, Neoplastic, 79-5220
 - Interferon
 - Antigens, Neoplasm, 79-5217
 - Histocompatibility Antigens, 79-5217
 - Membrane Proteins
 - Cell Transformation, Neoplastic, 79-5218
 - Mitomycin C
 - Virus Replication, 79-5209
 - Nucleotide Sequence
 - Deletion Mutants, 79-5213, 79-5214
 - Phospholipids
- Virus, SV40 (cont'd)**
 - Cell Adhesion, 79-5219
 - Prostatic Neoplasms
 - Adenocarcinoma, 79-4853
 - Radiation, Ionizing
 - Virus Replication, 79-5209
 - RNA, Messenger
 - Antigens, Neoplasm, 79-5211
 - Viral Proteins, 79-5211
 - Sialoglycoproteins
 - Isolation and Characterization, 79-5218
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - DNA Replication, 79-5216
 - s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-
 - RNA, Ribosomal, 79-5210
 - RNA, Viral, 79-5210
 - Viral Interference
 - Defective-Particle Mutants, 79-5221
 - Kidney Cells, Monkey, 79-5221
 - Viral Proteins, 79-5221
 - Virus, Adeno 2
 - Virus, Helper, 79-5215
 - Virus, Adeno 2 - SV40 Hybrid
 - DNA-RNA Hybridization, 79-5199
 - RNA, Viral, 79-5199
 - Virus, Helper
 - Antigens, Neoplasm, 79-5215
 - Deletion Mutants, 79-5215
- Virus, Turkey Herpes**
 - Virus, Marek's Disease Herpes
 - Immunity, Cellular, 79-5125
 - Viral Vaccines, 79-5125
- Virus, Varicella-Zoster**
 - Antigens, Viral
 - Lymphocyte Transformation, 79-5159
 - Carcinogenic Potential
 - Review, 79-4886
 - DNA, Viral
 - Isolation and Characterization, Review, 79-4887
 - Leukemia, Lymphoblastic
 - Pregnancy, 79-5267
 - Lymphoma
 - Interferon, 79-5159
 - Lymphocyte Transformation, 79-5159
- Virus, Vesicular Stomatitis**
 - Cell Fusion
 - Temperature Sensitive Mutants, 79-5232
 - Glycoproteins
 - Cell Fusion, 79-5232
 - Neuroblastoma
 - Cell Fusion, 79-5232
 - Plasmacytoma
 - RNA Replication, 79-5230
 - RNA, Messenger
 - Interferon, 79-5227
 - Ultraviolet Rays
 - RNA, Messenger, 79-5230
 - RNA Replication, 79-5230
 - Viral Proteins, 79-5230
- Virus, Visna**
 - Phosphono Formic Acid
 - Virus Replication, 79-5154
 - Phosphonoacetic Acid
 - Virus Replication, 79-5154
 - Phosphonoformic Acid, Trisodium Salt

- Virus, Visna (cont'd)**
 - Reverse Transcriptase, 79-5154
- Virus, Woolly Monkey**
 - Viral Proteins
 - Pseudotype Virus, 79-5141
 - Virus, Kirsten Murine Sarcoma
 - Virus, Helper, 79-5141
- Vitamin C**
 - see Ascorbic Acid
- Vitamin E**
 - Copper
 - Metabolism, Review, 79-4844
 - Free Radicals
 - Metabolism, Review, 79-4844
 - Lead
 - Metabolism, Review, 79-4844
 - Selenium
 - Metabolism, Review, 79-4844
 - Zinc
 - Metabolism, Review, 79-4844
- Vulvar Neoplasms**
 - Carcinoma, Epidermoid
 - Condylomata Acuminata, 79-5233
 - Condylomata Acuminata
 - Case Report, 79-5233
 - Leiomyosarcoma
 - Case Report, 79-5351
 - Neoplasm Recurrence, Local, 79-5351
- Water Pollution**
 - Aniline
 - Derivatives, 79-5020
 - Quantitation Method, 79-5020
- Wounds and Injuries**
 - Brain Neoplasms
 - Neoplasm Metastasis, 79-5109
 - Hepatoma
 - Neoplasm Metastasis, 79-5109
- Xeroderma Pigmentosum**
 - Purine, 2-Amino-6-methoxy-
 - Chromatids, Review, 79-4829
- Zearalenone**
 - Ames Test
 - Mutagenic Activity, 79-5029
 - Bacillus subtilis*
 - DNA, Bacterial, 79-5029
 - Mutagenic Activity, 79-5029
 - Bacillus thuringiensis*
 - Mutagenic Activity, 79-5029
 - Food Contamination
 - Body Fluids, Tissues, Cow, 79-5030
- Zeolite**
 - Environmental Hazard
 - Epidemiology, Review, 79-4811
- Zinc**
 - Ascorbic Acid
 - Metabolism, Review, 79-4844
 - Quinoline, 4-(Hydroxyamino)-, 1-Oxide
 - DNA, Binding, 79-5008
 - Tobacco
 - Heavy Metal Levels, 79-4944
 - Vitamin E
 - Metabolism, Review, 79-4844
- Zollinger-Ellison Syndrome**
 - Gastrointestinal Hormones
 - Diarrhea, 79-5309
 - Pancreatic Neoplasms
 - Case Report, 79-5076
 - Corticotropin, 79-5076

Chemical Abstracts Service Registry Number Index

36-06-6, 79-4959
 36-35-1, 79-4848
 50-00-0, 79-4835, 79-5220
 50-02-2, 79-5077
 50-03-3, 79-5144
 50-04-4, 79-4903, 79-5158
 50-06-6, 79-4836, 79-4958, 79-4959
 79-4965, 79-4984, 79-4990
 79-5022, 79-5057, 79-5063
 79-5064
 50-07-7, 79-5209
 50-18-0, 79-4817, 79-4994, 79-4995
 79-4998, 79-5079
 50-23-7, 79-5070, 79-5306
 50-24-8, 79-4994
 50-28-2, 79-5046, 79-5047, 79-5051
 79-5074, 79-5075, 79-5085
 79-5087
 50-29-3, 79-4963, 79-5095
 50-32-8, 79-4802, 79-4810, 79-4835
 79-4838, 79-4840, 79-4915
 79-4947, 79-4956, 79-4968
 79-5018, 79-5025, 79-5037
 79-5052, 79-5055, 79-5056
 79-5057, 79-5058, 79-5059
 79-5060, 79-5061, 79-5062
 79-5063, 79-5064, 79-5074
 79-5085, 79-5366
 50-44-2, 79-4994
 50-55-5, 79-4849
 50-76-0, 79-4839
 50-81-7, 79-4844
 51-18-3, 79-4221, 79-4835
 51-21-8, 79-5396
 51-31-0, 79-5072
 51-35-4, 79-5082
 51-45-6, 79-4842, 79-5081
 51-48-9, 79-4976
 51-79-6, 79-4835, 79-4982
 51-98-9, 79-5086
 53-16-7, 79-4985, 79-5051, 79-5074
 79-5383
 53-70-3, 79-5052
 53-79-2, 79-5057, 79-5231
 53-95-2, 79-4986
 53-96-3, 79-4864, 79-4907, 79-4963
 79-4985

54-11-5, 79-4830, 79-4845
 54-12-6, 79-4314, 79-4396, 79-4864
 54-25-1, 79-5396
 54-42-2, 79-5128, 79-5232
 55-18-5, 79-4828, 79-4990, 79-4991
 56-25-7, 79-4973
 56-49-5, 79-4840, 79-4918, 79-4990
 79-5025, 79-5052, 79-5053
 79-5054, 79-5063, 79-5065
 79-5073, 79-5074, 79-5075
 79-5235, 79-5248
 56-53-1, 79-4815, 79-4921, 79-4931
 79-5078, 79-5079, 79-5080
 79-5081, 79-5082, 79-5083
 56-55-3, 79-5100
 56-57-5, 79-4829, 79-5007
 56-65-5, 79-5065
 56-75-7, 79-5043, 79-5391
 57-30-7, 79-5068
 57-41-0, 79-4815
 57-63-6, 79-5086
 57-83-0, 79-5046, 79-5047, 79-5051
 79-5073
 57-88-5, 79-4928, 79-4985, 79-5074
 79-5399
 57-97-6, 79-4918, 79-5044, 79-5045
 79-5046, 79-5047, 79-5048
 79-5049, 79-5050, 79-5051
 79-5052, 79-5058, 79-5256
 79-5373
 58-08-2, 79-5057
 58-22-0, 79-4847, 79-4985, 79-5080
 58-61-7, 79-5393
 59-01-8, 79-5012
 59-02-9, 79-4844
 59-14-3, 79-4998, 79-5101, 79-5225
 59-87-0, 79-5000
 60-00-4, 79-5044, 79-5092
 60-11-7, 79-4907, 79-4985, 79-5021
 60-57-1, 79-5068
 60-92-4, 79-4842, 79-4937, 79-5072
 62-23-7, 79-5004
 62-44-2, 79-4815, 79-4818, 79-5006
 62-50-0, 79-4953, 79-5059
 62-53-3, 79-5020
 62-68-0, 79-4990

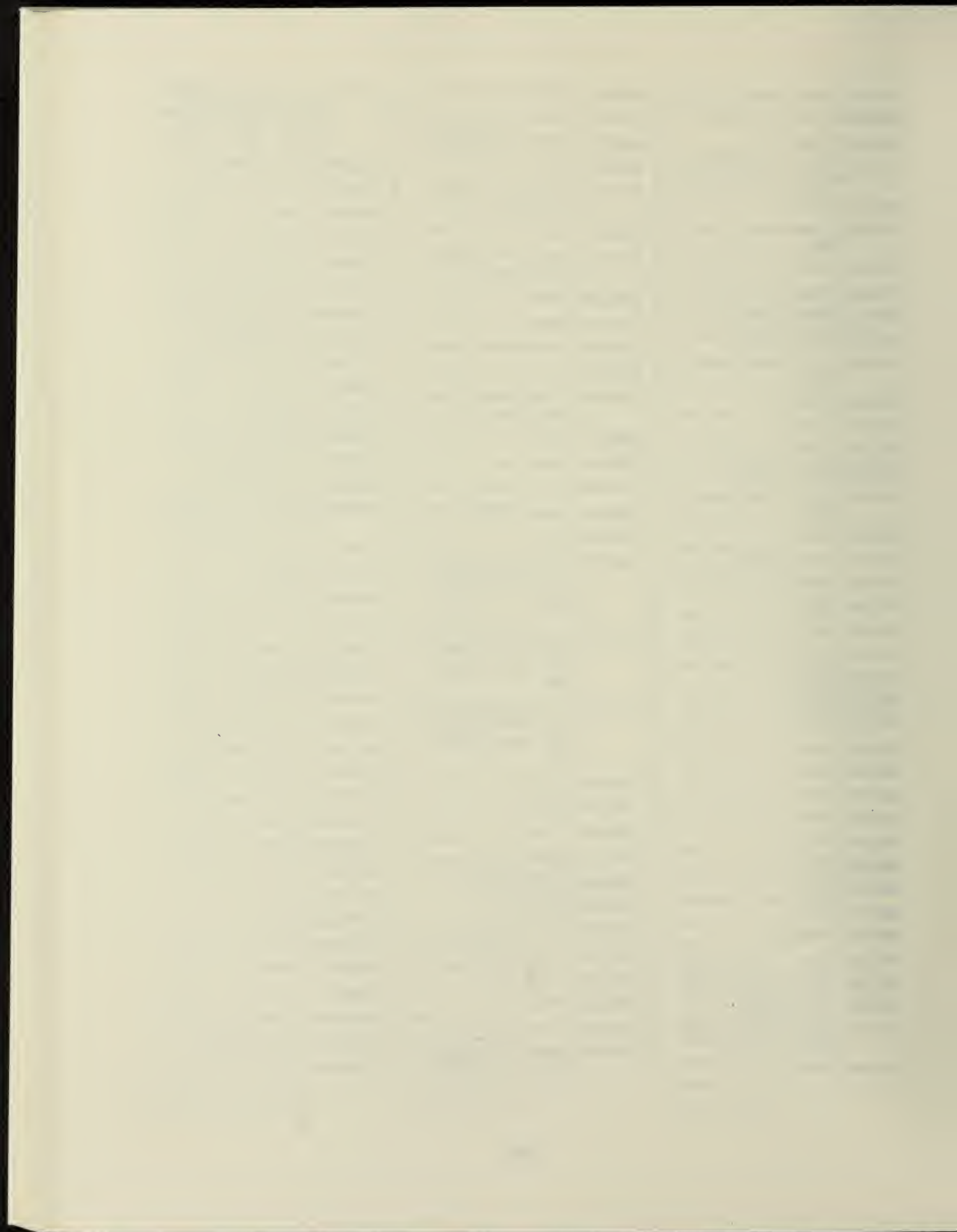
62-73-7, 79-4216, 79-4331
 62-75-9, 79-4828, 79-4988, 79-4989
 63-68-3, 79-5069
 64-17-5, 79-4823, 79-4836, 79-4918
 79-4924, 79-4956, 79-4958
 79-5004, 79-5313, 79-5355
 79-5356
 64-86-8, 79-5251, 79-5394
 66-27-3, 79-4835, 79-4952, 79-4953
 79-4996, 79-4998
 66-81-9, 79-4969, 79-5057, 79-5157
 79-5161, 79-5231
 67-20-9, 79-5000, 79-5009, 79-5010
 67-45-8, 79-5000
 67-63-0, 79-5313
 68-11-1, 79-5257
 68-76-8, 79-4834, 79-4835
 70-18-8, 79-5021, 79-5022
 70-25-7, 79-5001, 79-5002, 79-5059
 79-5200
 71-43-2, 79-4813, 79-4815, 79-4968
 79-5358
 71-58-9, 79-5354
 72-33-3, 79-5089
 73-22-3, 79-4314, 79-4396, 79-4864
 73-24-5, 79-5393
 75-01-4, 79-4808, 79-4813, 79-4920
 79-4958, 79-4959, 79-4962
 75-21-8, 79-4809, 79-4957
 75-35-4, 79-4959
 75-38-7, 79-4962
 75-52-5, 79-4976, 79-5018
 75-56-9, 79-4964
 79-01-6, 79-4920, 79-5375, 79-5376
 79-46-9, 79-4976
 81-07-2, 79-4864
 82-76-8, 79-4989
 85-01-8, 79-5037
 86-88-4, 79-4984
 91-20-3, 79-5037
 91-59-8, 79-4864, 79-5038, 79-5373
 92-87-5, 79-5373
 93-76-5, 79-4832
 94-58-6, 79-5023
 94-59-7, 79-5023

95-80-7, 79-5022	205-99-2, 79-5056, 79-5066	1083-48-3, 79-4999
96-45-7, 79-4833	206-44-0, 79-5066	1162-65-8, 79-5030, 79-5032, 79-5033 79-5034
100-52-7, 79-4823	207-08-9, 79-5056	1239-45-8, 79-5128
100-75-4, 79-4828	217-59-4, 79-5066	1309-37-1, 79-4947
101-14-4, 79-5024	226-36-8, 79-4947	1313-13-9, 79-4947
107-06-2, 79-4961	286-20-4, 79-4968	1314-20-1, 79-5110
107-07-3, 79-4957	289-95-2, 79-5396	1317-79-9, 79-4943
107-21-1, 79-4957	297-76-7, 79-5086	1318-02-1, 79-4811
107-30-2, 79-4813	298-01-1, 79-4972	1332-21-4, 79-4810, 79-4811, 79-4812 79-4813, 79-4815, 79-4830 79-4942, 79-4943, 79-4978 79-5369
108-91-8, 79-4970	298-81-7, 79-4861, 79-5093, 79-5099	1385-95-1, 79-5032
109-99-9, 79-4958	301-04-2, 79-4814, 79-4997	1403-66-3, 79-5012
110-44-1, 79-4975	302-01-2, 79-4835	1461-22-9, 79-5092
111-30-8, 79-5122	302-79-4, 79-5395	1606-67-3, 79-5038
113-52-0, 79-5010	303-47-9, 79-5030	1746-01-6, 79-4811, 79-4832, 79-5073 79-5095
115-02-6, 79-4999	305-03-3, 79-4994	1897-45-6, 79-4972
117-39-5, 79-5026	320-67-2, 79-5143	2279-76-7, 79-5092
120-12-7, 79-5037	434-07-1, 79-4847	2437-79-8, 79-4965
120-58-1, 79-5023	443-48-1, 79-4996	2613-02-7, 79-5258
121-69-7, 79-6262	446-86-6, 79-5042	2969-81-5, 79-5081
121-75-5, 79-4971	474-25-9, 79-4977	3083-23-6, 79-4965
123-91-1, 79-5095	512-56-1, 79-4816	3688-53-7, 79-5000
126-99-8, 79-4959, 79-4967	520-18-3, 79-5026	3817-11-6, 79-4864, 79-4992
128-37-0, 79-5074	521-18-6, 79-5046	4408-78-0, 79-5154, 79-5168, 79-5179
133-06-2, 79-4835	522-40-7, 79-5079	4637-56-3, 79-4829, 79-5007, 79-5008
134-32-7, 79-5038	525-03-1, 79-5038	4759-48-2, 79-4846
134-58-7, 79-4959, 79-5026	540-73-8, 79-4977	4885-02-3, 79-4813
139-05-9, 79-4864	545-55-1, 79-4835	5134-37-2, 79-5258
139-13-9, 79-4983	553-24-2, 79-4998	5139-02-6, 79-4834
143-67-9, 79-4994	610-49-1, 79-5038	5452-35-7, 79-4970
146-22-5, 79-5004	613-13-8, 79-5038	5957-20-0, 79-4990
147-85-3, 79-4997	615-53-2, 79-4978, 79-5373	6051-87-2, 79-5022, 79-5025, 79-5063
147-94-4, 79-5143, 79-5157, 79-5161	621-90-9, 79-5021	6098-44-8, 79-4829, 79-4986
150-68-5, 79-4972	645-12-5, 79-5000	6795-23-9, 79-5030
151-67-7, 79-4960	684-93-5, 79-4864, 79-5057, 79-5373	7241-98-7, 79-5032
153-78-6, 79-5038	759-73-9, 79-4979, 79-4980, 79-4981 79-4982, 79-5071	7439-89-6, 79-4944, 79-5095
154-17-6, 79-5077	794-93-4, 79-5011	7439-92-1, 79-4814, 79-4844, 79-4944
156-51-4, 79-5010	797-63-7, 79-5046	7439-95-4, 79-5082, 79-5132
156-54-7, 79-4966	817-99-2, 79-4999	7439-96-5, 79-4944, 79-5132
157-03-9, 79-4999	865-21-4, 79-5394	7440-02-0, 79-4813, 79-4948
189-55-9, 79-5059	908-35-0, 79-4958	7440-09-7, 79-5227
191-07-1, 79-5066	930-55-2, 79-4828	7440-23-5, 79-5227
191-24-2, 79-5056, 79-5066	979-92-0, 79-5393	
192-97-2, 79-5060	994-31-0, 79-5092	
193-39-5, 79-5056, 79-5066	1003-03-8, 79-4970	

7440-38-2, 79-4812, 79-4813
 7440-43-9, 79-4944
 7440-44-0, 79-4943
 7440-47-3, 79-4813, 79-4944, 79-4946
 79-5369
 7440-48-4, 79-5070
 7440-50-8, 79-4844, 79-4944, 79-4945
 79-5008
 7440-57-5, 79-5257
 7440-61-1, 79-4830, 79-4857, 79-5369
 7440-65-5, 79-4844, 79-4944, 79-5008
 7440-66-6, 79-4844, 79-4944, 79-5008
 7440-70-2, 79-4835, 79-4951, 79-5082
 79-5095
 7446-08-4, 79-4950
 7446-27-7, 79-4814
 7446-70-0, 79-5008
 7631-86-9, 79-4810, 79-4947
 7632-00-0, 79-4819, 79-4974, 79-4975
 79-5251
 7664-41-7, 79-5031
 7665-99-8, 79-4842, 79-4937
 7723-14-0, 79-5082
 7782-39-0, 79-5022
 7782-44-7, 79-4970
 7782-49-2, 79-4844
 7782-77-6, 79-4826
 7783-20-2, 79-4989
 7786-34-7, 79-4972
 7790-59-2, 79-4950
 7803-49-8, 79-5049
 8001-58-9, 79-5067
 8007-45-2, 79-5067
 8015-95-0, 79-5036
 8063-14-7, 79-5014
 8063-94-3, 79-4808
 9000-07-1, 79-5036
 9000-71-9, 79-5240
 9001-12-1, 79-5317
 9001-78-9, 79-4835, 79-5082, 79-5291
 9002-60-2, 79-5073, 79-5076
 9002-62-4, 79-4849, 79-4928, 79-5047
 79-5075
 9002-86-2, 79-4808

9002-93-1, 79-5229, 79-5785
 9003-98-9, 79-5191
 9004-10-8, 79-5077, 79-5144, 79-5159
 9007-12-9, 79-5300
 9008-11-1, 79-5129, 79-5173, 79-5217
 79-5227, 79-5241
 9008-18-8, 79-5002
 9035-50-1, 79-4814, 79-4840, 79-4843
 79-4956, 79-5038
 10101-21-0, 79-4951
 10102-18-8, 79-4950
 10102-43-9, 79-4320, 79-4342, 79-4960
 10212-25-6, 79-5143
 11028-71-0, 79-4905, 79-5254, 79-5255
 79-5259, 79-5394
 11033-22-0, 79-5393
 11056-06-7, 79-5091
 11089-65-9, 79-5116
 11097-69-1, 79-4984, 79-5060, 79-5078
 11118-26-6, 79-5116
 12001-28-4, 79-4810, 79-4811, 79-4812
 79-4813, 79-4815, 79-4830
 79-4942, 79-4943, 79-4978
 79-5369
 12001-29-5, 79-4810, 79-4811, 79-4812
 79-4813, 79-4815, 79-4830
 79-4942, 79-4943, 79-4978
 79-5369
 12172-73-5, 79-4810, 79-4811, 79-4812
 79-4813, 79-4815, 79-4830
 79-4942, 79-4943, 79-4978
 79-5369
 13010-47-4, 79-5046
 13422-55-4, 79-4949
 13454-96-1, 79-4949
 13967-73-2, 79-4951
 13981-16-3, 79-4857, 79-5098
 14596-10-2, 79-5106
 14808-60-7, 79-4943
 14930-96-2, 79-5077, 79-5251
 15519-61-6, 79-5393
 16056-34-1, 79-4811
 16543-55-8, 79-5013
 16561-29-8, 79-4837, 79-4838, 79-5041
 79-5077, 79-5216, 79-5256

17068-78-9, 79-4810, 79-4811, 79-4812
 79-4813, 79-4815, 79-4830
 79-4942, 79-4943, 79-4978
 79-5369
 17924-92-4, 79-5029, 79-5030
 18662-53-8, 79-4983
 19315-64-1, 79-4818
 19408-74-3, 79-5094
 20535-83-5, 79-4829
 21150-20-9, 79-5155, 79-5201
 21247-98-3, 79-5065
 21373-20-6, 79-5155, 79-5201
 21593-56-6, 79-5393
 22199-08-2, 79-4954
 22620-01-5, 79-5393
 23095-97-8, 79-5258
 23109-05-9, 79-5155, 79-5201
 23214-92-8, 79-4995
 24554-26-5, 79-4864, 79-4993, 79-5000
 79-5009
 24998-17-2, 79-5009
 25013-16-5, 79-5074
 25614-03-3, 79-5075
 25843-45-2, 79-4955
 26628-22-8, 79-5005
 28166-06-5, 79-5005
 28378-99-6, 79-5258
 29908-03-0, 79-5258
 37574-47-3, 79-5062, 79-5063
 40055-48-9, 79-4823
 42978-43-8, 79-5065
 51481-61-9, 79-5039, 79-5040
 52523-58-7, 79-5000
 53609-64-6, 79-5373
 53791-74-5, 79-5393
 54025-36-4, 79-5046
 57344-98-6, 79-5393
 57653-85-7, 79-5094
 59435-85-7, 79-4997
 59865-13-3, 79-4904
 59963-01-8, 79-5062, 79-5063
 63585-09-1, 79-5154



Wiswesser Line Notation Index

.AL..G3, 79-5008
 .AM, 79-5106
 .AS, 79-4812, 79-4813
 .AU, 79-5257
 .C, 79-4943
 .CA, 79-4835, 79-4951, 79-5082, 79-5095
 .CD, 79-4944
 .CO, 79-5070
 .CR, 79-4813, 79-4944, 79-4946, 79-5369
 .CU, 79-4844, 79-4944, 79-4945, 79-5008
 .D, 79-5022
 .FE, 79-4944, 79-5095
 .FE2.O3, 79-4947
 .K, 79-5227
 .KA2.SE-O2-Q2, 79-4950
 .MG, 79-5082, 79-5132
 .MN, 79-4944, 79-5132
 .MN..O2, 79-4947
 .NA, 79-5227
 .NA..N-O-Q, 79-4819, 79-4974, 79-4975, 79-5251
 .NA2.SE-O-Q2, 79-4950
 .NI, 79-4813, 79-4948
 .P, 79-5082
 .PB, 79-4814, 79-4844, 79-4944
 .PB3.P-O-Q3*2, 79-4814
 .PT..GGGG, 79-4949
 .PU, 79-4857, 79-5098
 .SE, 79-4844
 .SE..O2, 79-4950
 .SI..O2, 79-4810, 79-4943, 79-4947
 .SR, 79-4951
 .TH..O2, 79-5110
 .UR, 79-4830, 79-4857, 79-5396
 .Z&2.S-O4, 79-4989
 .ZN, 79-4844, 79-4944, 79-5008
 -HG-1, 79-4811
 E3VO2, 79-5081
 FYFU1, 79-4962
 G-SN-2&2&2, 79-5092
 G-SN-3&3&3, 79-5092
 G-SN-4&4&4, 79-5092
 GR CG DR BG DG, 79-4965

GR DMVN1&1, 79-4972
 GXGGYR DG&R DG, 79-4963, 79-5095
 GYEXFFF, 79-4960
 GYGU1, 79-4959
 GYGU1G, 79-4920, 79-5375, 79-5376
 GYGU1OPO&O1&O1, 79-4216, 79-4331
 G1O1, 79-4813
 G1U1, 79-4808, 79-4813, 79-4920, 79-4958, 79-4959, 79-4962
 G2G, 79-4961
 L B656 HHJ EMV1, 79-4864, 79-4907, 79-4963, 79-4985
 L B656 HHJ ENOV1&V1, 79-4829, 79-4986
 L B656 HHJ ENQV1, 79-4986
 L B666J, 79-5037
 L B666J HHJ EZ, 79-5038
 L B677 MV&T&J CO1 DO1 EO1 JMV1 NO1, 79-5251
 79-5394
 L C65 K666 1A TJ, 79-5056, 79-5066
 L C6566 1A PJ, 79-5066
 L C666J, 79-5037
 L C666J DZ, 79-5038
 L C666J EZ, 79-5038
 L D6 B66 P666 2AB A&J, 79-5059
 L D6 B666J, 79-5100
 L D6 B666J C1 J1, 79-4918, 79-5044, 79-5045, 79-5046
 79-5047, 79-5048, 79-5049, 79-5050, 79-5051
 79-5052, 79-5058, 79-5256, 79-5373
 L D6 B6666 2AB TJ, 79-4802, 79-4810, 79-4835, 79-4838
 79-4840, 79-4915, 79-4947, 79-4956, 79-4968
 79-5018, 79-5025, 79-5037, 79-5052, 79-5055
 79-5056, 79-5057, 79-5058, 79-5059, 79-5060
 79-5061, 79-5062, 79-5063, 79-5064, 79-5074
 79-5085, 79-5366
 L D6 B6666 2AB TJ H1Q, 79-5065
 L D6666 B6 2AB TJ, 79-5060
 L E5 B666 FVTTT&J E1 OQ, 79-4985, 79-5051, 79-5074
 79-5383
 L E5 B666 LUTJ A1 E1 FY&3Y QQ -B&AEFO, 79-4928
 79-4985, 79-5074, 79-5399
 L E5 B666 OV AHTTT&J A1 CQ E1 FV1Q FQ G1 -A&B -
 B&ACEFG
 79-5077
 L E5 B666 OV MUTJ A1 COV1 E1 FV1 L -A&L -
 B&ACEF
 79-5354
 L E5 B666 OV MUTJ A1 CQ E1 FV1Q FQ -B&ACEF
 79-5070, 79-5306

LIBRARY U. OF I. URBANA - CHAMPAIGN

L E5 B666 OV MUTJ A1 CQ E1 FV2VQ FQ -B&ACEF
 79-5144
 L E5 B666 OV MUTJ A1 E1 FQ -B&AEF, 79-4847, 79-4985
 79-5080
 L E5 B666 OV MUTJ A1 E1 FV1 -B&AEF, 79-5046
 79-5047, 79-5051, 79-5073
 L E5 B666 OVTJ A1 E1 FQ -A&M -B&AEF, 79-5046
 L E5 B666TJ A1 DQ E1 FY1&2VQ HQ, 79-4977
 L E5 B666TJ A1Q CQ E IQ MQ QQ F- DT5OV EHJ&
 OO- BT6OTJ CQ DQ EQ F
 79-4959
 L E5 B666TTT&J E1 FQ FIUU1 OQ, 79-5086
 L E5 B666TTT&J E1 FQ OQ, 79-5046, 79-5047, 79-5051
 79-5074, 79-5075, 79-5085, 79-5087
 L E5 D6656 1A T&&&T&J R1, 79-4840, 79-4918, 79-4990
 79-5025, 79-5052, 79-5053, 79-5054, 79-5063
 79-5065, 79-5073, 79-5074, 79-5075, 79-5235
 79-5248
 L E6 C5666 B6 3ABC VJ, 79-5056, 79-5066
 L G6 D6 B666J, 79-5052
 L5TJ AZ, 79-4970
 L6TJ AMSWO &-NA-, 79-4864
 L6TJ AMVNNO&2G, 79-5046
 L6TJ AZ, 79-4970
 L6UTJ A1 A1 BIUIY1&UZU1YU1VQ&1 C1 -T, 79-5395
 L6V DVJ B- C- E-/-AT3NTJ 3, 79-4834, 79-4835
 L66J, 79-5037
 L66J BMYZUS, 79-4984
 L66J BZ, 79-5038
 L66J CZ, 79-4864, 79-5038, 79-5373
 L666 B6 2AB PJ IZ, 79-5038
 L7TJ AZ, 79-4970
 NO, 79-4320, 79-4342, 79-4960
 ONN1&VO2, 79-4978, 79-5373
 ONN1&1, 79-4828, 79-4988, 79-4989
 ONN1YQ1&1YQ1, 79-5373
 ONN2&2, 79-4828, 79-4990, 79-4991
 ONN4&R, 79-4823
 ON1&UN1, 79-4955
 OO, 79-4970
 OV1 & 2-PB-, 79-4814, 79-4997
 QR BF DY2UY2R CF DQ EF& EF, 79-5084
 QR BQ DYQ1MY1&1 -L, 79-5072
 QR DY2& 2U, 79-4815, 79-4921, 79-4931, 79-5078, 79-5079
 79-5080, 79-5081, 79-5082, 79-5083
 QVYQYQVQ & 2 &621 T6NJ C1 2/XV/ &622, 79-4958
 QVYZ1OV1UNN &10/11, 79-4999
 QVYZ2S1, 79-5069

QVYZ2V1UNN -L &9/10, 79-4999
 QV1 3N, 79-4983
 QV1 3N &-NA- 3, 79-4983
 QV1N1VQ 22, 79-5044, 79-5092
 QV1OR BG DG EG, 79-4832
 QV1U2U2, 79-4975
 QV3R DN2G2G, 79-4994
 QY, 79-5313
 Q2, 79-4823, 79-4836, 79-4918, 79-4924, 79-4956, 79-4958
 79-5004, 79-5313, 79-5355, 79-5356
 Q2G, 79-4957
 Q2Q, 79-4957
 Q4N4&NO, 79-4864, 79-4992
 R, 79-4813, 79-4815, 79-4968, 79-5358
 SHX&1&1YZVQ -D, 79-4834
 SH1VQSHIVQ, 79-5257
 T B666 HKJ EZ H2 IR& LZ &E &9/26, 79-5128
 T C555 A AO DVOVTJ C1 G1, 79-4973
 T C566 DO LVOJ BO1, 79-4861, 79-5093, 79-5099
 T C6 B5665 2AB S BX IN QN NU JH&&TTTTJ FO1 I
 KVO1 KQ LOV1 M2 E- NT F6 E596 A
 BN LM&&TTJ NVO1 Q Q2, 79-5394
 T C666 BN INJ E1 F2 LN1&1 &GH, 79-4998
 T C666 BO EV INJ D1 FZ N1 G- K-/VM- OT5-16- AN
 FVN IVN LVO PVM SVTJ G1 JI KY
 NI RY 2, 79-4839
 T C676 BN&T&J B3N1&1 &GH, 79-5010
 T D3 B556 BN EM JV MVTTT&J GO1 H1OVZ KZ L1
 79-5209
 T D36 I666 B6 2AB U EOT&&&&J, 79-5062, 79-5063
 T E3 D5 C555 A D- FO KUTJ AG AG BG JG KG LG
 79-5068
 T E3 D6 B6666 2AB U FOTT&&&&J HQ IQ, 79-5062
 79-5063
 T F5 C6 B655 DOV GV OO QO RUT&&TTJ LO1, 79-5030
 79-5032, 79-5033, 79-5034
 T F6 C6 B655 DOV GVO PO ROT&&TTJ MO1, 79-5032
 T F6 D5 C666 EM ON&&TTTJ HO1 SOVR CO1 DO1
 EO1& TO1 UVO1
 79-4849
 T G6 D6 B666 CNJ, 79-4947
 T3NTJ A- 3PO, 79-4835
 T3OTJ, 79-4809, 79-4957
 T3OTJ B1, 79-4964
 T3OTJ GYGG, 79-4965
 T5M CNJ D2Z, 79-4842, 79-5081
 T5MTJ BVQ, 79-4997
 T5MVMV EHJ ER& ER, 79-4815

T5MYMTJ BUS, 79-4833
 T5N CNJ A2Q B1 ENW, 79-4996
 T5NTJ ANO, 79-4828
 T5NTJ ANW BOV1, 79-4997
 T5OJ BNW E- ET5N CSJ, 79-5000
 T5OJ BNW E- ET5N CSJ BMVH, 79-4864, 79-4993
 79-5000, 79-5009
 T5OJ BNW EIUN- AT5NVMV EHJ, 79-5000, 79-5009
 79-5010
 T5OJ BNW EIUN- AT5NVOTJ, 79-5000
 T5OJ BNW EIUNMVZ, 79-5000
 T5OJ BYVZU1- BT5OJ ENW, 79-5000
 T5OV EHJ CQ DQ EYQ1Q, 79-4844
 T50TJ, 79-4958
 T56 BM DN FN HNJ ISH, 79-4994
 T56 BM DN FN HNJ IZ, 79-5393
 T56 BMJ D1YZVQ -L, 79-4314, 79-4396, 79-4864
 T56 BN DN FN HNJ IZ D- BT5OTJ CQ DQ EIQ -A&CD
 79-5393
 T56 BN DN FNVNVJ B1 F1 H1, 79-5057
 T56 BO DO CHJ G1U2, 79-5023
 T56 BO DO CHJ G2U1, 79-5023
 T56 BO DO CHJ G3, 79-5023
 T56 BSVVMVJ, 79-4864
 T56 BVNV GUTJ CSXGGG, 79-4835
 T6MPOTJ BO BN2G2G, 79-4817, 79-4994, 79-4995, 79-4998
 79-5079
 T6MVMVJ EF, 79-5396
 T6N CN ENJ B- D- F-/- AT3NTJ 3, 79-4221, 79-4835
 T6N CNJ, 79-5396
 T6N CNJ BMSWR DZ &-AG-, 79-4954
 T6NJ C- BT5NTJ ANO, 79-5013
 T6NJ C- BT5NTJ A1, 79-4830, 79-4845
 T6NNVMVJ B- BT5OTJ CQ DQ EIQ -B&CD, 79-5396
 T6NTJ ANO, 79-4828
 T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C, 79-4998
 79-5101, 79-5225
 T6NVMVJ E1 A- ET5OTJ B1Q CQ -A&C, 79-5128, 79-5232
 T6NVN ENJ DZ A- BT5OTJ CQ DQ EIQ, 79-5143
 T6NVNJ DZ A- BT5OTJ CQ DQ EIQ, 79-5143, 79-5157
 79-5161
 T6O DOTJ, 79-5095
 T6VMVMV FHJ F2 FR, 79-4836, 79-4958, 79-4959, 79-4965
 79-4984, 79-4990, 79-5022, 79-5057, 79-5063
 79-5064
 T6VMVMV FHJ F2 FR &-NA-, 79-5068

T6VMVTJ EIYQ- BL6VTJ D1 F1, 79-4969, 79-5057
 79-5157, 79-5161, 79-5231
 T66 BM DN FN HNJ IS- ET5N ONJ DNW, 79-5042
 T66 BNJ BO EMQ, 79-4829, 79-5007, 79-5008
 T66 BNJ BO ENW, 79-4829, 79-5007
 T66 BO EVJ CR CQ DQ& DQ GQ IQ, 79-5026
 T66 BO EVJ CR DQ& DQ GQ IQ, 79-5026
 T66 BVOT&J D1 GG IVMYVQ1R& JQ, 79-5030
 T666 BO IO T&&J EG FG LG MG, 79-4811, 79-4832
 79-5073, 79-5095
 T666 BO IOT&&J DG EG FG KG LG MG, 79-5094
 T666 BO IOT&&J DG EG FG LG MG NG, 79-5094
 T67 GMV JN IHJ CNW KR, 79-5004
 VHH, 79-4835, 79-5220
 VHR, 79-4823
 VHIYQYQYQ1Q -BAA -D, 79-5077
 VH3VH, 79-5122
 WNMYUM&N1&NO, 79-5001, 79-5002, 79-5059, 79-5200
 WNR BF ENUNUN, 79-5005
 WNR CNW DNUNUN, 79-5005
 WNR DVQ, 79-5004
 WNR DYQY1QM VYGG -DL, 79-5043, 79-5391
 WNY, 79-4976
 WN1, 79-4976, 79-5018
 WS1&O1, 79-4835, 79-4952, 79-4953, 79-4996, 79-4998
 WS1&O2, 79-4953, 79-5059
 ZH, 79-5031
 ZQ, 79-5049
 ZR, 79-5020
 ZR BG D- 21, 79-5024
 ZR CZ D1, 79-5022
 ZR DR DZ, 79-5373
 ZVN1&NO, 79-4864, 79-5057, 79-5373
 ZVN2&NO, 79-4979, 79-4980, 79-4981, 79-4982, 79-5071
 ZVO2, 79-4835, 79-4982
 ZV1MV1UNN, 79-4999
 ZZ, 79-4835
 1MM1, 79-4977
 1MR DNUNR, 79-5021
 1N1&R, 79-6262
 1N1&R DNUNR, 79-4907, 79-4985, 79-5021
 1OPO&O1&O1, 79-4816
 1UYG1U1, 79-4959, 79-4967
 1X1&1&R BQ CX1&1&1 E1, 79-5074
 1Y1&1R BQ EO1, 79-5074

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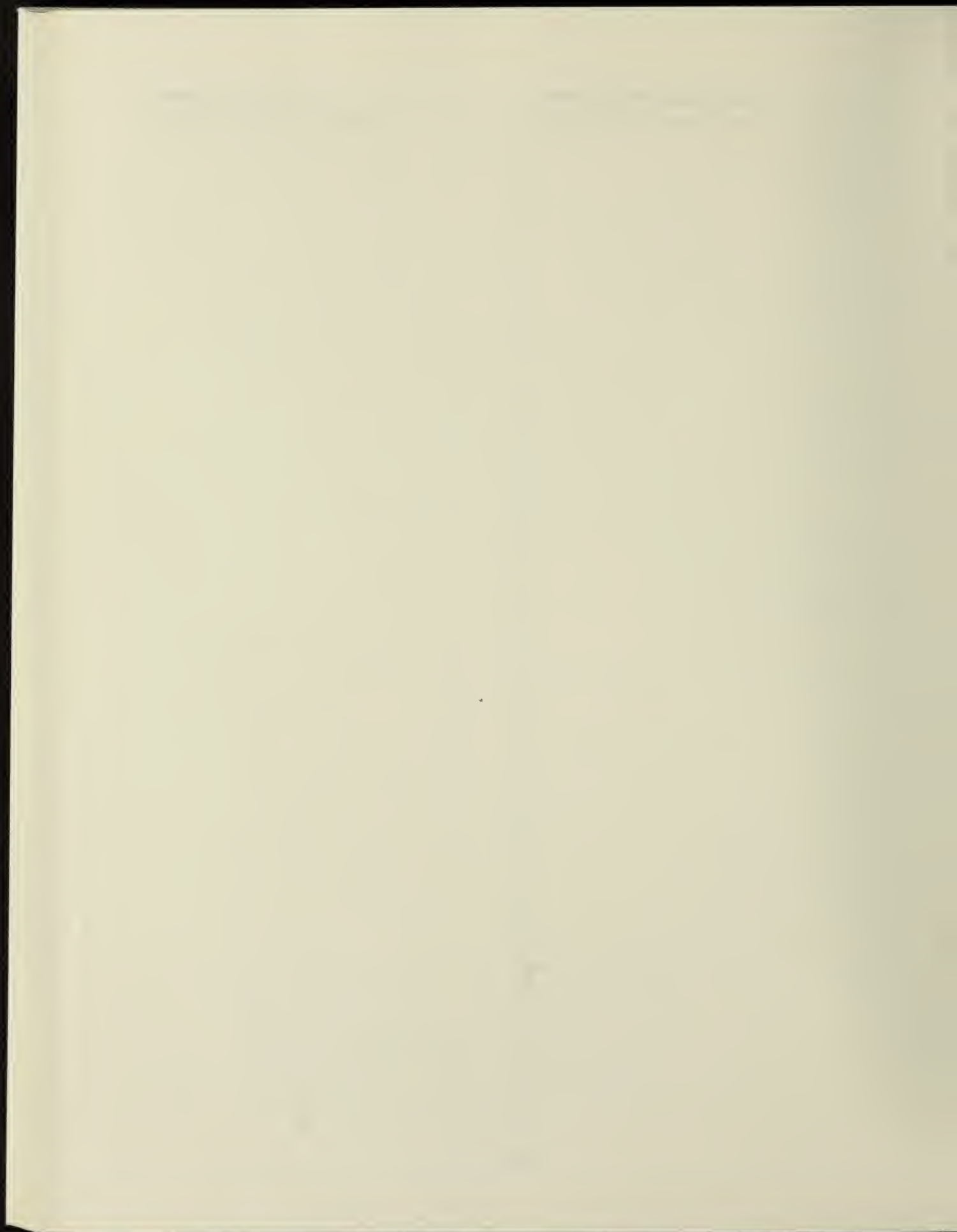
1Y1&1R CQ FO1, 79-5074

2OR DMV1, 79-4815, 79-4818, 79-5006

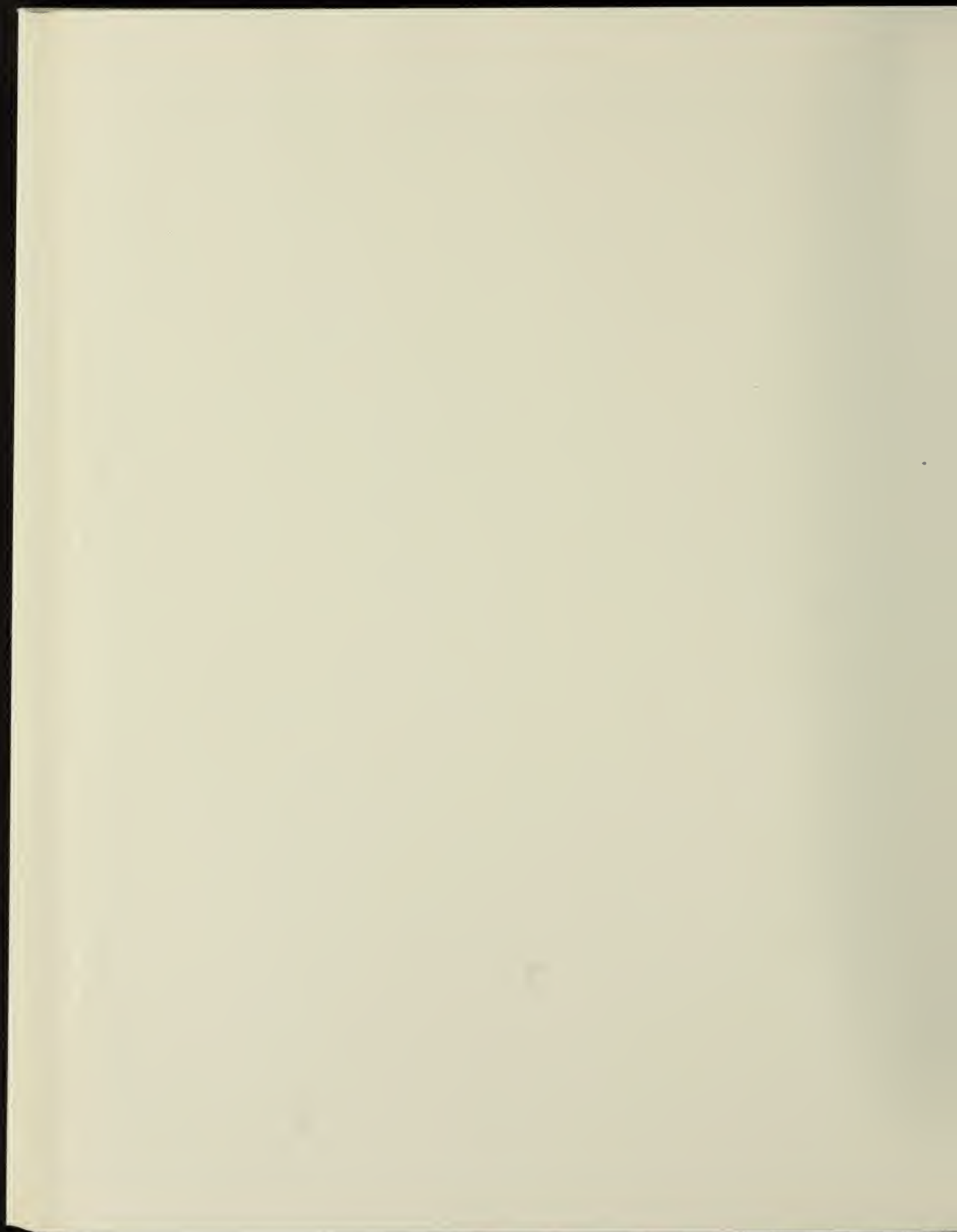
2OV1YVO2&SPS&O1&O1, 79-4971

3XR&R&VO2N2&2 &GH, 79-4990

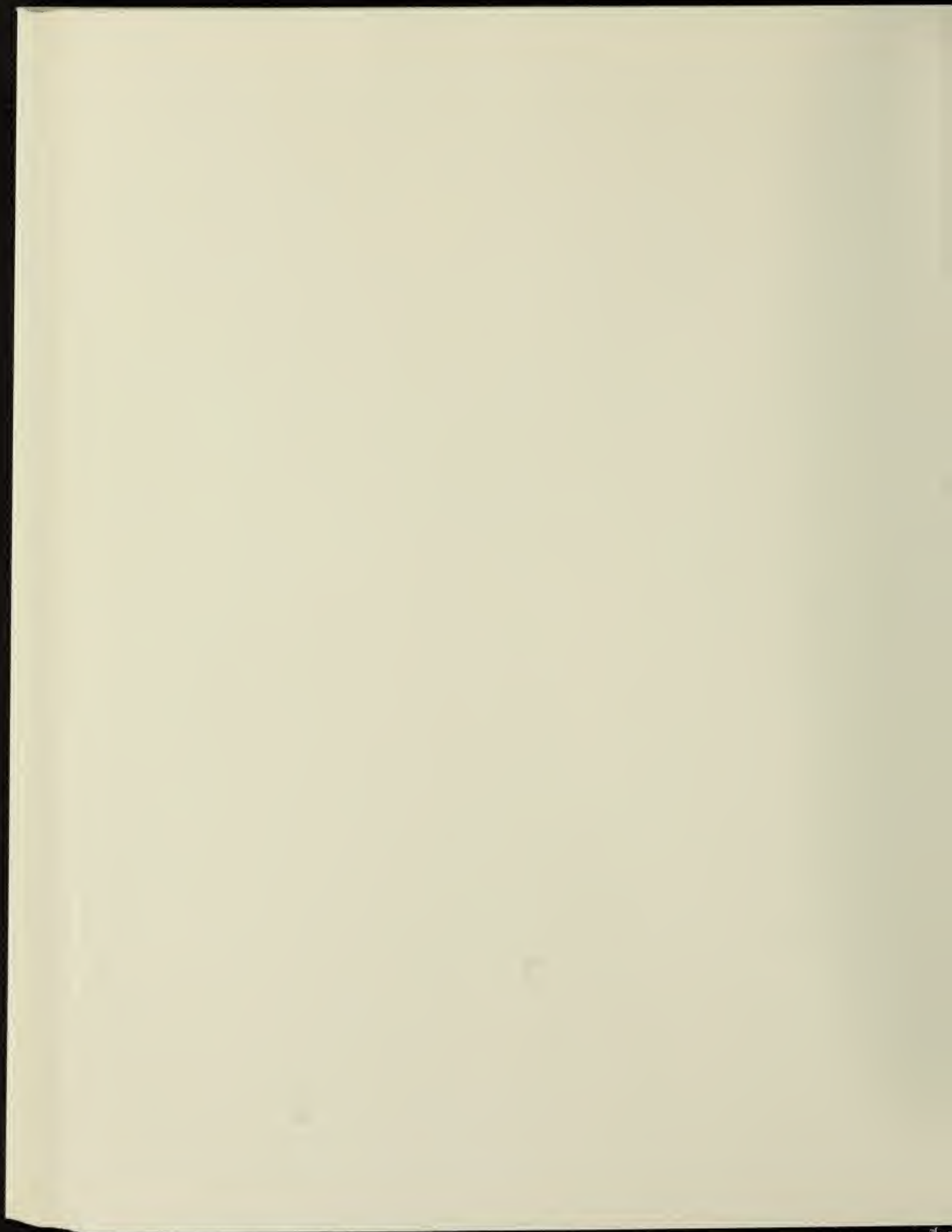
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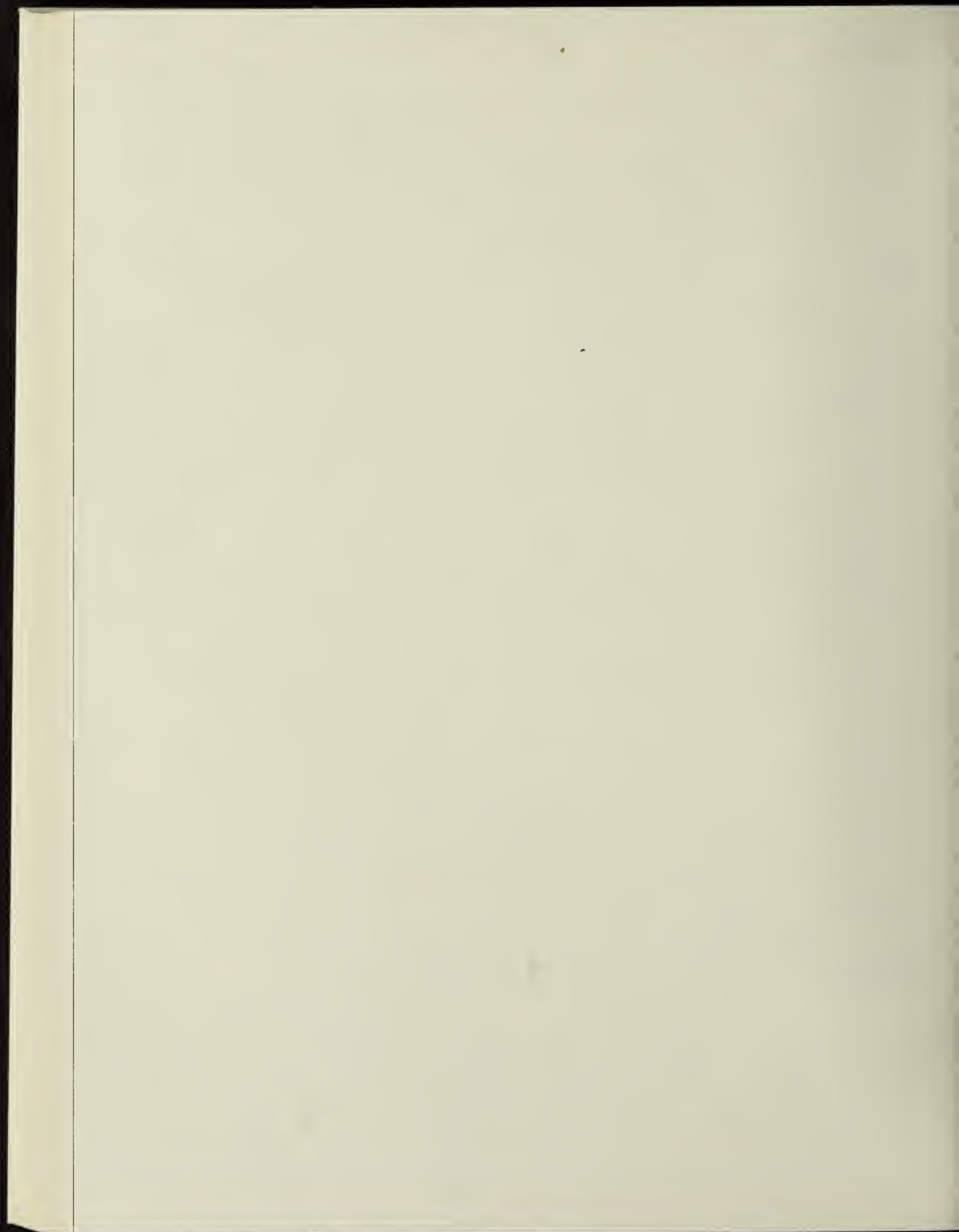
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VOLUME 17, ISSUE 10

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page Nos.
REVIEW	(Rev)	79-5401—79-5511	2161
CHEMICAL CARCINOGENESIS	(Chem)	79-5512—79-5674	2182
PHYSICAL CARCINOGENESIS	(Phys)	79-5675—79-5697	2217
VIRAL CARCINOGENESIS	(Viral)	79-5698—79-5822	2222
IMMUNOLOGY	(Immun)	79-5823—79-5850	2250
PATHOGENESIS	(Path)	79-5851—79-5925	2256
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	79-5926—79-5975	2268
MISCELLANEOUS	(Misc)	79-5976—79-6000	2277
AUTHOR INDEX			2283
SUBJECT INDEX			2289
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2327
WISWESSER LINE NOTATION INDEX			2331

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT₁	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT₁	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		

REVIEW

- 79-5401 Assessment of Trichloroethylene as an Occupational Carcinogen. (Eng) Page, N. N. (Priorities and Res. Analysis Branch, National Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD 20857). *IARC Sci Publ* (25): 75-79; 1979.

Decisions made by the National Institute for Occupational Safety and Health (NIOSH) regarding trichloroethylene (TCE) when it was found to be carcinogenic in mice are reviewed. The compound is used mainly in the vapor degreasing of metal parts, and it is estimated that over 100,000 workers (degreaser operators) are exposed to high levels of TCE. An additional 3.5 million workers are exposed to lower levels in other occupations. The carcinogenic effect may occur through a highly reactive epoxide which has a very short half life. There is a definite species difference in ability to metabolize TCE to the epoxide. Rats, which do not develop cancer after exposure to TCE, have a lower capacity for metabolizing the chemical to the epoxide. Epidemiological studies in Sweden on 750 workers exposed for more than 10 yr have not shown an increased risk for cancer, but this group is small statistically and the duration of exposure too short for ruling out carcinogenicity in humans. NIOSH has concluded that TCE is potentially carcinogenic in the workplace, but only weakly so. The present standard of 100 ppm in the US is considered to be too high, and a level of 25 ppm is recommended on the basis of the evidence available. (no refs)

- 79-5402 Food Additives, Drugs, and Pesticides. (Eng) Davis, W. (Research Training and Liaison Unit, International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Rosenfeld, C. *IARC Sci Publ* (25): 173-175; 1979.

A discussion of symposium papers dealing with the carcinogenic risks of food additives, drugs, and pesticides is summarized. Evidence was presented that compounds such as phenobarbital, which causes hepatic nodules in mice and rats, and 4,4'-dichlorodiphenyltrichloroethane, also carcinogenic in animals, may be noncarcinogenic in humans. Nevertheless, a very cautious approach has been assumed by agencies such as the US Occupational Safety and Health Administration, which proposes that positive animal data on carcinogenicity should supersede human data and that a significantly increased incidence of tumors in treated animals should be interpreted as evidence of carcinogenicity regardless of spontaneous cancer incidence. A number of agents cause hepatomas in mice, and the question has been raised as to whether these nodules are malignant or not. Regulations concerning risk-benefit of additives, drugs, and pesticides are not always consistent, and efforts are under way in the US and Europe to improve government regulation. (no refs)

- 79-5403 Carcinogenic Risk of Products Used in the Pharmaceutical and Related Industries. (Eng) Coustou, F. (Univ. Bordeaux II, Bordeaux, France). *IARC Sci Publ* (25): 129-149; 1979.

The problems, in France, of regulating drugs to eliminate or cur-

tail potential carcinogenicity are reviewed. Some carcinogens may be introduced during the manufacturing process, such as asbestos during filtration, vinyl chloride in aerosol production or packaging, or 2-naphthylamine and other aniline compounds during the dyeing process. The use of artificial sweeteners in the manufacture of foodstuffs is banned in France. At present, general regulations of the French government for the pharmaceutical industry state that agents should be tested for carcinogenicity prior to marketing only if: (1) the agent is closely analogous to known carcinogens or cocarcinogens; (2) a suspicion of carcinogenicity has been aroused during long-term toxicological testing; (3) the drug is to be administered over long periods of time. (22 refs)

- 79-5404 The Asbestos Industry and Statutory Control of its Hazards. (Eng) Newhouse, M. L. (IUC Centenary Occupational Health, London School Hygiene and Tropical Medicine, London, England). *IARC Sci Publ* (25): 59-70; 1979.

Data on the causal relationship between asbestos and respiratory disease, especially lung cancer, are reviewed. Pneumoconiosis related to asbestos exposure was reported in the 1920's, about 40 yr after the first asbestos factories were established in the United Kingdom and the US. The risk of lung cancer was first noted in the 1930's and established definitively by epidemiological studies in 1955 (the risk for exposed workers was nine times greater than that for the general population). An act regulating the asbestos industry was passed by the British Parliament in 1969. An advisory panel had found that bronchial carcinoma was a complication of asbestosis rather than of asbestos exposure, mesothelial tumors were linked to asbestos exposure, and crocidolite asbestos rather than chrysotile asbestos was the cause of the mesotheliomas. Beginning in 1971, clinical examinations were offered to all workers in the asbestos industry, and by 1974, nearly 7,000 workers had been examined. Three recent studies indicate that there may be a dose-response relationship between asbestos and lung cancer. On the basis of these studies, standards on asbestos exposure have been or are being revised. (11 refs)

- 79-5405 Role of Selenium in the Chemoprevention of Cancer. (Eng) Griffin, A. C. (Dept. Biochemistry, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX). *Adv Cancer Res* 29: 419-442; 1979.

The role of selenium in the chemoprevention of cancer is reviewed. The topics included are the toxicology and pathology of Se, the nutritional aspects of Se (Se-responsive diseases, requirements for Se as a micronutrient, interactions of Se with other minerals in nutrition), Se as a causative factor or carcinogen in early reports, the lack of useful chemotherapeutic effects of Se on cancer growth, the effect of Se on carcinogenesis (inhibition of azo dye hepatocarcinogenesis), the biological functions of Se (as a cofactor for formate dehydrogenase, glycine reductase, and glutathione peroxidase), and the possible mechanisms of action of Se in the inhibition of carcinogenesis (decreasing the mutagenicity of various carcinogens, effects on carcinogen metabolism, protection of cells

against aberrant oxidative damage, and the stages of initiation or promotion of carcinogenesis affected by Se). (76 refs).

- 79-5406 Is Sodium Azide Preservative a Carcinogen (Letter to Editor)? (Eng) Liu, T. Z. (Center Advanced Medical Technology, San Francisco State Univ., San Francisco, CA 94132). *Clin Chem* 25(8): 1514-1515; 1979.

Sodium azide was a very potent mutagen in the Salmonella/microsome test system. Because there is a high (90%) correlation between carcinogenicity and mutagenicity in this system, sodium azide should be considered a potential carcinogen. (8 refs)

- 79-5407 Development, Growth Rate, Degree of Malignancy, and Chromosome Pattern of Morris Transplantable Hepatomas. (Eng) Morris, H. P. (Dept. Biochemistry, Howard Univ. Coll. Medicine, Washington, DC); Slaughter, L. J. *J Toxicol Environ Health* 5(2/3): 433-452; 1979.

A review is presented of the induction of Morris transplantable hepatomas in inbred Buffalo and ACI rats by various carcinogens, including N-2-fluorenyldiacetamide (2-FdiAA), N-2-fluorenylphthalamic acid (2-FPA), 2-(4'-methyl)benzoylamino fluorene, fluorenyl-2,7-disuccinamic acid, 2,4,6-trimethylaniline, 4'-fluoro-4-biphenylacetamide N-fluorenyl-2-nicotinamide, and aflatoxin B₁ (AFB₁). Growth, histology, and metastatic patterns of the tumor cell lines between 1973 and 1976 were investigated. Most of the tumors demonstrated a remarkably stable growth rate; some which had started slowly grew even more slowly in 1976, and some that had intermediate growth rates grew more slowly in 1973 than in 1976. The percentage distribution of six aneuploid hepatomas is presented. A haploid and a hyperdiploid line were the most homogeneous cell lines. The karyotype of each hepatoma line had a consistent number of abnormal chromosomes. Of the 48 tumor lines investigated, 31 demonstrated lung metastases in two transplant generations. Of 17 tumors induced by 2-FdiAA, 10 had lung metastases, 10/12 induced by 2-FPA had lung metastases, as did 3/5 induced by AFB₁. (25 refs)

- 79-5408 Environmental Chemical Carcinogens and Liver Cancer. (Eng) Linsell, C. A. (Interdisciplinary Programme and International Liaison Unit, International Agency Res. Cancer, Lyon, France). *J Toxicol Environ Health* 5(2/3): 173-181; 1979.

Chemical carcinogens that have been implicated in the etiology of human liver cancer are appraised. The liver carcinogens considered are those available to humans as contaminants of food and water or as additives. Naturally occurring liver carcinogens include mycotoxins [aflatoxins (AF's), cyclochlorotine, luteoskyrin, sterigmatocystin], pyrrolizidine alkaloids (isatidine, lasiocarpine, monocrotaline, and retrorsine), cycasin, safrole, and tannic acid. Synthetic liver carcinogens include nitrosamines and nitrosamides and chlorinated hydrocarbons (organochlorines, polychlorinated biphenyls, carbon tetrachloride, chloroform). The AF's are probably the most investigated group of chemical liver carcinogens. These compounds are among the most potent naturally occurring hepatocarcinogens. Considerable evidence has accumulated

relating their ingestion to human disease. Doses of a few parts per billion produce liver cancers in susceptible animals, and even single doses produce cancers in rats 1 yr after ingestion. However, there are marked differences among animal species, and continuous feeding for 6 yr is required to produce tumors in monkeys. Data from field studies in Mozambique, Thailand, Kenya, and Swaziland are summarized. AF intakes were recorded from food only; however, it was difficult to assess the intake of home-brewed beer made from cereals and of groundnuts, which are eaten irregularly as snacks. Therefore, the estimated intakes, which ranged from 3.5 nanograms (ng)/kg·day in Kenya to 222 ng/kg·day in Mozambique, must be considered as minimal. The crude liver cancer rate correlated with AF intake in the study areas. The association was observed in widely separated geographic areas, and no evidence of a contrary nature, ie, well-documented high levels of Af exposure paralleled by a low frequency of liver cancer, has been reported. (24 refs)

- 79-5409 Chemistry of N-Nitrosamides and Related N-Nitrosamino Acids. (Eng) Chow, Y. L. (Dept. Chemistry, Simon Fraser Univ., Burnaby, British Columbia, Canada V5A 1S6). *ACS Symp Ser* (101): 13-37; 1979.

Differences in the reaction patterns of nitrosamides and nitrosamines when thermolyzed or photolyzed are discussed in relation to their ground state electronic configurations. At -150°C, a singlet excited state of a nitrosamide undergoes radiationless decay to afford a thermally unstable isomer that is readily dissociated by a second photon to the amidyl and nitric oxide radicals. Studies of nitrosamide photolysis by flash excitation provided kinetic rate constants of the resultant amidyl reactions, from which β -elimination was shown to arise from both the bimolecular reaction of the amidyl radical with the nitrosamide and a unimolecular elimination. (44 refs)

- 79-5410 N-Nitrosamines as Environmental Carcinogens. (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701). *ACS Symp Ser* (101): 165-173; 1979.

Investigations of the carcinogenic activity of N-nitrosamines are reviewed. Entirely different tumors are induced by these compounds in rats and in hamsters. The relative effectiveness of these compounds varies greatly, even between structurally closely related compounds. The relationship between human cancers and exposure to N-nitroso compounds has been difficult to establish. The major contribution to carcinogenic risk is probably through the in vivo formation of N-nitroso compounds by the reaction of amines with nitrite. The principal source of nitrite in the stomach is cured meats, and the rate of formation of N-nitroso compounds is proportional to the square of the nitrite concentration. The most favored site for the formation of carcinogenic N-nitroso compounds by reaction with secondary and tertiary amines is the stomach, with its acid conditions. Studies in which an amine and nitrite were fed simultaneously to laboratory animals are reviewed. Several of the amine-nitrite combinations formed carcinogenic N-nitroso derivatives, but others did not; however, these non-carcinogenic combinations cannot be considered definitive. Several of the amine-nitrite combinations that were negative in the rat test were positive in the Ames mutagenicity test, which is more sensitive than long-term animal bioassays. (31 refs)

- 79-5411 A Survey of Methods for the Determination of Non-volatile Nitrosamines in Foods. (Eng) Kubacki, S. J. (Dept. Instrumental Analysis, Inst. Fermentation Industry, ul. Rakowiecka 36, Warsaw, 12, Poland). *Pure Appl Chem* 51(6): 1369-1373; 1979.

Methods for determining total and individual nonvolatile nitrosamines in foods are reviewed. The most widely accepted method for estimating total nonvolatile nitrosamines is one that efficiently splits the N-NO group. The nitrite formed is determined after reaction with sulfanilamide and N-(1-naphthyl)ethylenediamine. Complete elimination of water from the reaction medium is essential. It is likely that the most profitable approach to determining individual nonvolatile nitrosamines is through the use of high-pressure liquid chromatography (HPLC). Coupling the thermal energy analyzer with HPLC allows the simultaneous determination of volatile and nonvolatile nitrosamines. (45 refs)

- 79-5412 Quantitative Aspects of Exposure and Mechanism in N-Nitrosamine Carcinogenesis. (Eng) Wishnok, J. S. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02138). *ACS Symp Ser* (101): 153-163; 1979.

Variations in carcinogenic potency of the N-nitrosodialkylamines (nitrosamines) are examined quantitatively both in terms of environmental exposure and formation and in the context of the mechanism through which nitrosamines initiate cancer. The relative risks of these compounds is discussed in terms of nitrosamines in cooked bacon. The typical range of concentration of nitrosamines in processed meats is 3-25 ppb for N-nitrosodimethylamine (NDMA), 2-12 ppb for N-nitrosodiethylamine (NDEA), and 5-50 ppb for N-nitrosopyrrolidine (NP). Relative potencies have been assigned to these compounds in BD rats: 7 for NDMA, 6 for NDEA, and 1 for NP. The structure-activity relationships of the nitrosamines were investigated. Computerized multiple regression analyses were performed on the acyclic nitrosamines, using $\log(1/D_{50})$ where D_{50} is the mean carcinogenic dose, as the dependent variable analogous to the relative biological response. It is shown that most of the variation in carcinogenicity within the series of acyclic nitrosamines can be associated with water-hexane partition coefficients and electronic inductive effects of substituents on the α -carbons. These methods may be useful in predicting carcinogenicity and as tools for probing mechanisms of carcinogenicity. (34 refs)

- 79-5413 N-Nitrosamines in Consumer Products and in the Workplace. (Eng) Krull, I. S. (New England Inst. Life Sciences, 115 Second Ave., Waltham, MA 02154); Edwards, G.; Wolf, M. H.; Fan, T. Y.; Fine, D. H. *ACS Symp Ser* (101): 175-194; 1979.

Data on the presence of N-nitroso derivatives in pharmaceuticals, commercial cutting fluids, cosmetics, skin lotions and shampoos, and herbicides are reviewed. Seventy-three prescription and over-the-counter drugs were analyzed by gas chromatography-thermal energy analysis and/or high-pressure liquid chromatography-thermal energy analysis. For most of the drug products, there does not appear to be a serious problem with regard to the presence of N-nitroso contaminants. Relatively high concentrations (0.02%-2.99%) of N-nitrosodiethanolamine (NDEIA) were found in com-

mercial cutting fluids. Since NDEIA causes cancer in two species of laboratory animals, cancer incidence among exposed workers should be studied. NDEIA levels in cosmetics ranged from trace amounts to 49,000 nanograms (ng)/g; in lotions, from 0 to 140 ng/g; and in shampoos from 0 to 260 ng/g. Further investigation is necessary to determine the exposure of beauty care and industrial workers to N-nitroso compounds via these products. In various herbicides, dimethylnitrosamine was present in concentrations ranging from 0 to 40 ppm, and dipropylnitrosamine was present at 0 to 195 ppm. Five out of six 2,4-dichlorophenoxyacetic acid herbicides contained DMN at levels between 250 and 650 μ g/liter. The results of thermoelectron analyses of various commercial products (pesticides, meat products, cosmetics, cutting fluids) are presented. The most frequently observed N-nitroso derivative was NDEIA. (64 refs)

- 79-5414 Tobacco Specific N-Nitrosamines: Occurrence, Carcinogenicity, and Metabolism. (Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Chen, C. B.; McCoy, G. D.; Hoffmann, D. *ACS Symp Ser* (101): 125-152; 1979.

The relationship between tobacco-specific N-nitrosamines and the various cancers associated with tobacco usage, including cancer of the lung, oral cavity, esophagus, pancreas, and bladder, is reviewed. The major tobacco-specific nitrosamines derived from tobacco alkaloids include N'-nitrososornicotine (NNN) and 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Both compounds are found in relatively high concentrations in mainstream and sidestream tobacco smoke and in unburned processed tobacco. The major precursor for both compounds is nicotine. NNN induces esophageal and nasal cavity tumors in rats, tracheal tumors in hamsters, and lung adenomas in strain A mice. NNK is more tumorigenic than NNN in strain A mice. The activation pathway for NNN and nitrosopyrrolidine (NPY) may be metabolic α -hydroxylation, since electrophilic diazohydroxides and carbonium ions are generated upon decomposition of the unstable intermediates α -hydroxy-NPY, 2'-hydroxy-NNN, and 5'-hydroxy-NNN. In *Salmonella typhimurium*, the synthetic precursors to these intermediates, α -acetoxy-NPY, 2'-acetoxy-NNN, and 5'-acetoxy-NNN, were mutagenic without activation. After hydrolysis, the products of α -acetoxy compounds were all detected as metabolites of NNN and NPY. Products similar to those from α -hydroxylation of NNN were obtained from the metabolic α -hydroxylation of NNK. The role of these intermediates in carcinogenesis induced by NPY, NNN, and NNK is currently being studied. (56 refs)

- 79-5415 Gastric Cancer in Patients Who Have Taken Cimetidine (Letter to Editor). (Eng) Elder, J. B. (Dept. Surgery, Univ. Manchester, Royal Infirmary, Manchester M13 9WL, England); Ganguli, P. C.; Gillespie, I. E. *Lancet* 2(8136): 245; 1979.

Comments regarding an earlier article postulating a possible link between cimetidine (CM) therapy and gastric carcinoma are reviewed. It is not known whether CM is nitrosated in vivo, but the nitrosated compound derived from CM in vitro is analogous to N-methyl-N'-nitro-N-nitrosoguanidine. Also, the manufacturers have stated that CM can be nitrosated and that the nitrosocimetidine produced in vitro is mutagenic. Although early cancer research suggested that the period of latency between exposure to a potential carcinogen and the diagnosis of gastric car-

cinoma is several years, recent work with nitroso compounds in laboratory animals does not support the necessity of such a long latent period. Carcinomas can be readily produced in animals by the administration of nitroso compounds or their precursors in such tests. A recent publication reported a 5.36% incidence of gastric carcinoma in a group of patients after operations for duodenal ulcer, but not in unoperated patients. Any method used to reduce gastric acid secretion may increase the incidence of malignant change in the gastric mucosa. (24 refs)

- 79-5416 Gastric Cancer in Patients who Have Taken Cimetidine (2 Letters to Editor). (Eng) Mullen, P. W. (Dept. Pharmacology, Materia Medica and Therapeutics, Univ. Manchester, Stopford Building, Manchester M13 9PT, England); Guslandi, M. *Lancet* 1(8131): 1406; 1979.

Possible explanations for the development of gastric carcinoma in three previously reported patients who had taken cimetidine (CM) for dyspeptic symptoms are presented. A previous speculation on the existence of a carcinogenic N-nitroso derivative of CM in the stomach is unlikely. If the cancer was related to nitrosamines, their existence could have been due to the presence of salivary and gastric thiocyanate if the patients were smokers, to the consumption of thiocyanate- or nitrite-containing foods, or to the consumption of other drugs that can be nitrosated in acidic environments containing nitrite. In addition, if a connection between CM and gastric cancer is to be discussed, the effects of CM on gastric mucus glycoproteins should be borne in mind. (9 refs)

- 79-5417 Carcinogenicity of Lindane. (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD 21701). *Environ Res* 19(2): 460-481; 1979.

A review of every study on the carcinogenicity of lindane in animals was attempted. Lindane is highly carcinogenic in rats and mice. It induced benign and malignant neoplasms at all sites in male and female rats. Adrenal and pituitary carcinomas were increased markedly in male and female rats. Females were more susceptible than males. Ovarian carcinomas were increased in lindane-treated female rats. There were increased incidences of hepatic neoplasms in both sexes. Hepatic carcinomas were induced in four strains of mice. The incidence of hepatic neoplasms was markedly increased in CF1 strain mice. Rats (particularly males) given lindane also developed toxic lesions as a result of treatment. These lesions included interstitial fibrosis of the kidney and atrophy of the testes. They may have interfered with the development of neoplasms in male rats. (20 refs)

- 79-5418 Toluene. A Toxicologic Review. (Eng) Cohr, K. H. (Arbejdsmiljøinstituttet, Baunegardsvej 73, DK-2900 Hellerup, Denmark); Stokholm, J. *Scand J Work Environ Health* 5(2): 71-90; 1979.

The application, metabolism, toxicologic mechanisms, effects on specific organs, mutagenicity, carcinogenicity, biological indicators of exposure, and dose-response relationship of toluene are reviewed. In one study, the majority of 401 patients with lymphoid leukemia, bone marrow aplasia, myeloid leukemia, and myelofibrosis had been exposed to benzene and toluene. (150 refs)

- 79-5419 Time and Dose Factors in Carcinogenesis (Letter to Editor). (Eng) Brodsky, A. (P.O. Box 34471, W. Bethesda, MD 20034). *Health Phys* 36(3): 468-471; 1979.

The use of an analytical stochastic model for calculating and plotting graphs of the incidence of animals with tumors vs time is reported, and the results are compared with recently published results using an empirical lognormal model. For certain ranges of the parameters, the analytical model will also predict what appear to be lognormal curves of tumor probability vs time, similar to those plotted with the empirical model. However, the tumor incidence vs time curves with this model do not approximate lognormality. These curves are for situations in which the carcinogen is more rapidly removed from the animal's tissue, and thus there is no carcinogen present in later life to continue the first or second transitions toward the tumor state. The analytical model can also demonstrate lognormal-appearing graphs for a response vs dose curve, and it can also demonstrate the various shapes of the lognormal model that approximate linearity in some cases and S-shaped functions in other cases. The analytical model is not an empirical lognormal function but is, instead, an expression derived from integration from assumptions regarding the form of the probability of a first transition and the conditional probability of a second transition. Approx linear as well as S-shaped functions are consistent with the analytical model, depending on the particular carcinogen and its instantaneous probabilities and on whether the exposure is long-term or relatively acute. (6 refs)

- 79-5420 Carcinogenesis in Urogenital Sites. (Eng) Paulson, D. F. (Duke Univ. Medical Center, P.O. Box 2977, Durham, NC 27710). *Invest Urol* 16(2): 77-86; 1978.

An overview of carcinogenesis in urogenital sites is presented under the headings normal cellular control mechanisms, theories of carcinogenesis, chemical carcinogens, irradiation-induced carcinogenesis, viral carcinogenesis, viruses and human tumors, renal adenocarcinoma, and bladder and prostatic cancer. (128 refs)

- 79-5421 Changes in Mammalian Sperm Morphology after X-Ray and Chemical Exposures. (Eng) Wyrobek, A. J. (Biomedical Sciences Div., Lawrence Livermore Lab., Univ. California, Livermore, CA 94550). *Genetics* 92(Suppl, part 1): S105-S119; 1979.

Relevant concepts in studies of sperm morphology (SM), including morphological and genetic factors in sperm shaping and the effects of chemical and physical agents on SM, are reviewed. SM in mammals provides a unique approach to quantitating the effects of environmental agents on germ cells. In unperturbed male mice, the sperm of each genotype can be reproducibly characterized by the shape of the head, the overall percent of sperm with head-shape abnormalities, and the types of abnormalities seen. Genetic studies show that sperm shape is highly heritable and that the fraction of abnormal sperm is controlled by a multitude of autosomal factors plus, probably, involvement of the sex chromosomes. Exposure to ionizing radiation or to certain chemical agents in vivo leads to dosage-dependent increases in the fraction of sperm with head-shape abnormalities. These results are documented in numerous mammalian species, including humans. Evidence from mouse studies suggests that sperm shape is affected by mutagenic agents. Since sperm samples are easily obtained and SM can be rapidly quantitated, these observations suggest that SM in the mouse may

REVIEW

be an applicable screen for environmental effects on germ cells. Changes in sperm are also seen in the offspring of male mice exposed to radiation or chemical alkylating agents. Preliminary evidence suggests that these changes represent heritable sperm shape abnormalities that can be further transmitted to subsequent generations. The problems of determining the genetic implications of induced sperm abnormalities in exposed males are discussed. SM testing may have a direct application to humans. (63 refs)

- 79-5422 Carcinogen Prediction in the Laboratory: A Personal View. (Eng) Garner, R. C. (Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England). *Proc R Soc Lond [Biol]* 205(1158): 121-134; 1979.

Short-term chemical carcinogenicity tests based on the hypothesis that all carcinogenic chemicals are electrophiles or must be metabolically converted to electrophiles are reviewed and compared with traditional methods. In vitro tests include nucleic acid reactions (for detection of electrophilic metabolites) in prokaryotes or in eukaryotes and sebaceous gland suppression or nonspecific esterase activity in sebaceous glands of mouse skin (for polycyclic hydrocarbons only). In vivo tests include the use of strain A mice for scoring lung adenomas, scoring the numbers of transformed cells taken from hamster fetuses after carcinogen administration to the mother, culture and examination of organs taken from treated animals, and the use of density gradient centrifugation to detect DNA damage in vivo. Compared with long-term animal studies, these short-term tests should enable large numbers of chemicals to be screened rapidly and inexpensively. (56 refs)

- 79-5423 Possibilities and Limits of the Ames Test. (Ger) Dehnen, W. (No affiliation given). *Lufthyg Silikoseforsch* 11: 81-87; 1978.

The possibilities and limitations of the mutagenicity and carcinogenicity testing of chemicals in the Ames Salmonella mutagenicity assay are weighed. The test is simple, rapid, and inexpensive. However, the result cannot be freely extrapolated to in vivo conditions. It is only with some reservations that carcinogenicity can be inferred from the mutagenicity found in the assay, because about 90% of all substances tested are both mutagenic and carcinogenic; a negative response does not rule out the carcinogenicity of a given substance. Also, there is no definite correlation between the intensity of the two effects. (14 refs)

- 79-5424 Bacterial Tests for Potential Carcinogens. (Eng) Devoret, R. (No affiliation given.). *Sci Am* 241(2): 40-49; 1979.

New short-term bacterial tests, including the Ames test, the inductest, and the lambda mutatest, for identifying environmental agents that cause DNA damage and for clarifying the mechanism of DNA damage are described. Induction of a dormant bacterial virus, prophage lambda, is detected in the inductest. In the mutatest, a modified form of the prophage makes plaques on a lawn of *Escherichia coli* when it undergoes mutation. The enzyme-induction test is a biochemical counterpart of the inductest. (no refs)

- 79-5425 'Human' and 'Animal' Carcinogens. (Eng) Teichmann, B. (Dept. Chemical Carcinogenesis, Central Inst. Cancer Res., Acad. Sciences GDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany); Schramm, T. *IARC Sci Publ* (25): 203-206; 1979.

The terms human carcinogen and animal carcinogen are discussed in relation to cancer research, prevention, and control legislation. A chemical demonstrated to be carcinogenic in animals should be considered to represent a risk to humans. However, nonexperts tend to consider that animal carcinogens produce cancer only in animals and can be neglected with regard to the human situation. These terms should either be avoided or used only in the context of generally accepted and available definitions. (9 refs)

- 79-5426 Chemical Hepatitis. Pathogenesis, Detection and Management. (Eng) Tamburro, C. H. (Div. Digestive Diseases and Nutrition, Dept. Medicine, Sch. Medicine, Health Sciences Center, Univ. Louisville, Louisville, KY 40232). *Med Clin North Am* 63(3): 545-566; 1979.

Information concerning the pathogenesis, detection, and management of drug- and chemical-induced hepatotoxicity is reviewed. Tables listing chemicals carcinogenic in humans and possible and actual occupational hepatotoxins are given. (24 refs)

- 79-5427 Residues of Carcinogenic Animal Drugs in Food: Difficulties in Evaluation of Human Safety. (Eng) Somogyi, A. (Dept. Drugs, Animal Nutrition and Residue Res., Federal Office Health, Thiel-allee 88-92, 1000 Berlin 33, W. Germany). *IARC Sci Publ* (25): 123-127; 1979.

Permissible levels of potentially carcinogenic drug residues in animals destined for human consumption are reviewed. The appearance of new analytical methods with high sensitivity and specificity permits the detection of residues at the parts/billion level. The parts/trillion level may soon be reached. There are scientists who argue the case for zero tolerance for carcinogens in food. It is suggested, however, that the relative carcinogenic risk of consuming animals with drug residues should be compared with that of smoking a single cigarette or eating a charcoal-broiled steak. The benefits presently gained from drugs that cure and prevent infections and parasitic diseases in food-producing animals should make the presence of very low levels of these drugs or their metabolites in the human diet acceptable. (no refs)

- 79-5428 Decision on the Control of a Dietary Carcinogen-Aflatoxin. (Eng) Linsell, C. A. (International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France). *IARC Sci Publ* (25): 111-122; 1979.

The discovery of aflatoxin as a carcinogen is reviewed. Suspicions were first aroused when poultry and fish fed mold-contaminated peanuts and/or feeds developed turkey "X" disease and liver cancer, respectively. Laboratory investigations of the carcinogenicity of aflatoxins were carried out in a wide range of animals, and marked differences in species susceptibility were noted. Field studies in Africa and Asia showed a significant correlation between estimated av daily adult intake of aflatoxin and the incidence of liver cancer. The staple foods of most of the

developing countries are at risk for aflatoxin contamination, as are many of their exports to developed countries. Peanuts, used for human and animal consumption, are particularly at risk. Permissible limits for aflatoxin contamination of foodstuffs of 21 countries are tabulated, along with permissible limits set by the Council of the European Economic Community for aflatoxin B₁ in animal feed. Regulatory actions on aflatoxins taken by industrialized countries do not protect the food supplies of indigenous populations of countries producing crops most likely to become contaminated because of a conducive climate. (no refs)

- 79-5429 The Approach of the European Communities to the Assessment of the Carcinogenic Risk of Environmental Chemicals, in Particular, Artificial Colourings. (Eng) Bourdeau, P. (Directorate General Res., Science and Education, Commission European Communities, 200 rue de la Loi, 1040 Brussels, Belgium); Ott, H.; Haigh, R. *IARC Sci Publ* (25): 101-109; 1979.

A brief outline is given of the rationale of the Environmental Research Program of the European Economic Community (EEC) and of its implementation. The major part of the program is devoted to research on the exposure-effect relationships for mutagens and carcinogens and to the establishment of criteria. As a first step, a battery of test systems for mutagenicity screening is being established. These will be evaluated in a comparative test program. In a discussion of EEC legislative actions on food colorings, the criteria used by the Scientific Committee for Food to classify and evaluate coloring agents are listed. Proposed regulatory action includes the classification of agents as unacceptable, temporarily acceptable, and acceptable. (no refs)

- 79-5430 Extraction of Trace Amounts of Organic Compounds from Water with Porous Organic Polymers. (Eng) Dressler, M. (Inst. Analytical Chemistry, Czechoslovak Acad. Sciences, 611 42 Brno, Czechoslovakia). *J Chromatogr* 165(2): 167-206; 1979.

A concentration technique for analyzing low concentrations of organic water pollutants is described. The technique is based on the sorption of organic compounds on organic porous polymers. The principles of the method, the characteristics and applications of various types of sorbents, the quality requirements for the materials used, and the sensitivity of the method are discussed. (115 refs)

- 79-5431 Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks. Report of the Interagency Regulatory Liaison Group, Work Group on Risk Assessment. (Eng) U.S. Environmental Protection Agency (Interagency Regulatory Liaison Group, Room 500, 1111 18th Street, N.W., Washington, DC 20207). *J Natl Cancer Inst* 63(1): 241-268; 1979.

A description is given of (1) the basis for the qualitative evaluation of a particular substance for potential carcinogenicity and how the results of epidemiological studies and animal bioassays, along with other types of information, are used in making that evaluation; and (2) methods used for quantitative estimates of the carcinogenic risk posed by the substance, if these risk estimates are required. Three types of evidence can be used to identify potential car-

cinogens: (1) epidemiologic evidence from studies of exposed human populations, (2) experimental evidence from long-term bioassays on animals, and (3) supportive or suggestive evidence from studies of chemical structure or from short-term or other tests known to correlate with carcinogenicity. Scientific bases for accepting evidence from these three sources are delineated, along with factors that should be considered in evaluating experimental and epidemiologic data. The experimental design and conduct of animal studies influence the evaluation of these studies. Ways of evaluating data from experimental animal studies of widely varying content and quality for purposes of identifying carcinogens are presented. Certain carcinogenic responses observed in experimental animals may not be predictive of human response. Current methodologies for the quantification of risk are described. There are mathematical models that can extrapolate, within a biologic system, cancer incidence data observed at experimental dose levels to estimate risks at the (usually much lower) levels that are of concern for humans. Factors that should be considered in attempts to identify the human population(s) at risk and to define their conditions and levels of carcinogen exposure are also presented. Possible methods of correlating the magnitude of effects observed in one human population or in experimental animals with the magnitude of effects in the human population for which the estimate of risk is being made are given. Limitations in current risk estimation methodologies are described, as are the problems of ensuring that human risk is not underestimated. Finally, the issue of thresholds for carcinogens is reviewed. (127 refs)

- 79-5432 Review of Pesticide Carcinogenesis Data and Regulatory Approaches. (Eng) Saffiotti, U. (Experimental Pathology Branch, Div. Cancer Cause and Prevention, NCI, Bethesda, MD). *IARC Sci Publ* (25): 151-166; 1979.

Carcinogenicity data are presented for 47 pesticides evaluated in the IARC Monograph series. These pesticides have been both poorly and scantily tested for carcinogenicity. Additional tests have been carried out under the NCI Carcinogenesis Program, and detailed results of the bioassays are published in the NCI Carcinogenesis Technical Report Series. Preliminary reports are published in the Federal Register. In a review of regulatory approaches to pesticides, international activities are outlined and examples are given of factors, such as public concern, scientific work, and governmental response, contributing to the development of such regulations. The problem of risk assessment has been approached from many sides, but it remains largely unsolved. Besides risks and benefits, an essential component in evaluation is the analysis of technological alternatives. Two other factors are public documentation of the process of evaluation and registration of environmental carcinogens and their uses. Reduction of exposure to environmental carcinogens to a minimum feasible level depends on social, economic, and temporal factors and implies the acceptance of a finite level of risk. (36 refs)

- 79-5433 Epidemics of Non-Infectious Disease. (Eng) Lawther, P. J. (MRC Toxicology Unit, Clinical Section, St. Bartholomew's Hosp. Medical Coll., Charterhouse Square, London EC1M 6BQ, England). *Proc R Soc Lond [Biol]* 205(1158): 63-75; 1979.

Noninfectious diseases that have been associated with exposure to carbon tetrachloride, polycyclic aromatic hydrocarbons, asbestos, mercury, and dioxin are reviewed. 1,2,5,6-Dibenzanthracene and 3,4-benzpyrene were the first known carcinogenic hydrocarbons;

REVIEW

these and other polycyclic aromatic hydrocarbons have been associated with skin and lung cancers. Carcinoma of the bronchus and pleural and peritoneal mesotheliomata have been associated with asbestos exposure, and cigarette smoking has been shown to be a synergistic factor. An increase in liver tumors has been reported in Vietnam and is thought to be related to dioxin exposure. (47 refs)

- 79-5434 Carcinogenicity of Endrin. (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD 21701). *Sci Total Environ* 12(2): 101-135; 1979.

The carcinogenicity of the chlorinated hydrocarbon insecticide endrin is reviewed. Endrin is carcinogenic for rats and, most likely, mice and dogs. When fed in the diet, it caused significant incidences of malignant neoplasms at all sites. In one study, female rats were susceptible to the development of neoplasms of the endocrine organs, particularly carcinomas of the adrenal and pituitary glands, as well as neoplasms of the reproductive system. In other studies, female rats tended to have carcinomas of the endocrine system, mammary gland, and reproductive system, and males and females tended to have lymphomas. Rats developed unusual malignant neoplasms, such as Kupffer cell sarcomas of the liver and sarcomas of the mammary gland, uterus, and stomach. There also were toxic changes, particularly in male rats. These lesions included interstitial fibrosis of the kidney; polyarteritis of the mesenteric, pancreatic, and other arteries; and atrophy of the testes. Such lesions generally interfered with the health of the rats and with the development of neoplasms. Dogs receiving endrin for 2 yr had bone marrow hyperplasia (HP), lesions of the thyroid gland, and lesions of the skeletal muscle. They also had mild or diffuse HP of the liver; mild atrophy of the testes; focal HP of the prostate gland; HP, adenoma, or carcinoma of the parathyroid gland; and occasional fibrosis of the spleen. One female dog had an early carcinoma of the thyroid gland. Mice ingesting endrin developed increased incidences of carcinoma of the liver and sarcoma of the uterus. (29 refs)

- 79-5435 Studies of Reserpine and Breast Cancer in Rochester, Minnesota. (Eng) Labarthe, D. R. (Dept. Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN); O'Fallon, W. M. In: *Epidemiological Issues in Reported Drug-induced Illnesses - S.M.O.N. and Other Examples*. Proceedings of an international symposium held 19-21 January 1976, Honolulu, HI. Gent, M.; Shigematsu, I., eds. (Hamilton, Canada: McMaster University Library Press): 337 pp.: 91-98; 1978.

Two studies of reserpine and breast cancer, both based on the medical record linkage system for the population of Rochester, Minnesota, are reviewed. Neither the retrospective case-control study nor the prospective cohort study of hypertensive women supports the hypothesis of an association between reserpine use and breast cancer. The fundamental methodological features of these studies are described in relation to definition of the agent and illness in question, the selection of subjects for study, and the ascertainment of exposure to the agent and the occurrence of disease. A conceptual scheme is suggested for considering successive stages of the scientific and policy issues involved, and the fundamental importance of the methodological issues is emphasized. (12 refs)

- 79-5436 Drug-induced Chronic Hepatic Disease. (Eng) Zimmerman, H. J. (Veterans Admin. Medical Center, 50

Irving St., N.W., Washington, DC 20422). *Med Clin North Am* 63(3): 567-582; 1979.

The induction of chronic active hepatitis, subacute hepatic necrosis, steatosis, phospholipidosis, vascular hepatic lesions, hepatic granulomas, cirrhosis, noncirrhotic portal hypertension, and neoplasms by various drugs is reviewed. The relationships between liver adenoma or carcinoma and oral contraceptives and between hepatic angiosarcoma and vinyl chloride or thorium dioxide exposure are discussed. (75 refs)

- 79-5437 Congenital Malformations and Other Reproductive Hazards from Environmental Chemicals. (Eng) Sullivan, F. M. (Dept. Pharmacology, Guy's Hosp. Medical Sch., St. Thomas St., London SE1 9RT, England); Barlow, S. M. *Proc R Soc Lond [Biol]* 205(1158): 91-110; 1979.

Possible adverse effects of chemical exposure on reproduction are discussed, and data concerning the reproductive outcome after exposure to chemicals in the workplace or environment are reviewed. Exposure of men to environmental chemicals may lead to cancer in their offspring; a study of 386 children dying from malignant disease before 5 yr of age showed a significant excess of fathers in hydrocarbon-related occupations. The association between vaginal cancer and prenatal diethylstilbestrol exposure has been established. Angiosarcomas have been reported in offspring of pregnant rats exposed to vinyl chloride monomer. Other possible transplacental carcinogens include anesthetics and irradiation. (103 refs)

- 79-5438 Mechanism of Action of Estrogen Antagonist: Relationship to Estrogen Receptor Binding and Hyperestrogenization. (Eng) Clark, J. H. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX 77030); Hardin, J. W.; McCormack, S. A.; Padykula, H. A. *Prog Cancer Res Ther* 10: 107-133; 1978.

The relationship of estrogen receptor binding and hyperestrogenization to the mechanism of action of estrogen antagonists is reviewed, and a new classification is proposed for estrogen agonists and antagonists. Estriol is a short-acting estrogen and, hence, acts as a partial agonist-antagonist when injected. However, when it is implanted, it acts as an agonist with no antagonistic properties. Thus, estriol, along with dimethylstilbestrol, mesobutoestrol, and 16-oxoestradiol, are classified as short-acting estrogens. The long-acting estrogens are divided into two classes, A and B, according to their retention times in the body. Subclass A includes estradiol and diethylstilbestrol (DES), because both of these hormones are fully agonistic, with no antagonistic properties, and they have similar nuclear retention times and biologic potencies. Subclass B includes nonsteroidal estrogen antagonists such as Nafoxidine, CI-628, and Clomid, because of their ability to stimulate estrogenic function over longer periods of time than estradiol or DES and yet manifest antagonistic properties when given as multiple injections. (50 refs)

- 79-5439 Oestrogen Replacement Therapy (2 Letters to Editor). (Eng) Greenblatt, R. B. (Medical Coll. Georgia, Augusta, GA 30901); Gambrell, R. D.; Sturdee, D. W. *Lancet* 1(8131): 1398-1399; 1979.

Two letters point out that an editorial concerning the risk of endometrial cancer in patients on hormone-replacement therapy fails to mention recent reports claiming that the addition of cyclic courses of a progestagen at monthly intervals reduces the incidence of endometrial cancer. (19 refs)

- 79-5440 Tumorigenic Aspects. (Eng) Kirk, M. E. (Dept. Pathology, Montreal General Hosp., 1650 Cedar Ave., Montreal, Canada H3G 1A4). *Int J Gynaecol Obstet* 16(6): 473-478; 1979.

Tumors (except those of the pituitary) that have been reported to occur in women taking combined oral contraceptive (OC) preparations are reviewed. Tumors of the cervix (dysplasia and its progression to carcinoma in situ), liver (focal nodular hyperplasia and liver cell adenomas), and breast (fibroadenoma, fibrocystic disease, and carcinoma) are considered with respect to pathologic features, both gross and microscopic, and differential diagnosis. The principal focus of the review is on the liver. There is a bewildering array of hepatic lesions, with considerable problems of nomenclature and pathogenesis, but it is likely that only two pathologically distinct lesions occur: focal nodular hyperplasia (FNH) and liver cell adenoma (LCA). FNH has been well-described, but its etiology and pathogenesis remain undetermined. LCA has also been well-described and, although its etiology remains undetermined, there is general agreement that it is a benign neoplasm. It is premature to draw conclusions about a relationship between OC's and liver tumors. Although the endocervical mucosa is very responsive to hormones and many women who use OC's have a reversible hyperplasia of the endocervical epithelium, the effects of OC's on the cervix cannot be fully evaluated until further prospective studies are carried out. The same breast diseases occur regularly in both users and nonusers of contraceptive hormones. The findings of several large studies have so far refuted any relationship between breast disease and OC use. Because many carcinogens have a lengthy latency period, final conclusions must await longer-term, more well-designed studies. (33 refs)

- 79-5441 Serious Adverse Reactions to Oral Contraceptives. (Eng) Mann, J. I. (Dept. Social Medicine, Oxford Univ., 8 Keble Rd., Oxford OX1 3QN, England). In: *Epidemiological Issues in Reported Drug-induced Illnesses - S.M.O.N. and Other Examples*. Gent, M., Shigematsu, I., eds. (Hamilton, Ontario: McMaster University Library Press) 337 pp.: 59-68; 1978.

Studies that suggest an association between oral contraceptive (OC) use and fatal adverse reactions to these preparations are summarized. A comparison between fatality rate resulting from their use and mortality from complications of unwanted pregnancies in women using a less effective method of contraception (diaphragm) suggests that fatal adverse reactions to OC's account for a greater number of deaths. Forty-six cases of benign liver adenoma and one case each of hepatocellular carcinoma and hepatoblastoma have been described in women using OC's. An increased risk of breast cancer has been described in a case-control study of certain high-risk users. (18 refs)

- 79-5442 Oral Contraceptives and Neoplasia. (Eng) Huggins, G. R. (Dept. Obstetrics and Gynecology, Hosp. Univ.

Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104); Giuntoli, R. L. *Fertil Steril* 32(1): 1-23; 1979.

Available data regarding possible associations between oral contraceptives (OC) and human neoplasia are reviewed in light of the pregnancy risk or benefit of oral contraception. The principal investigative methods in the human are: case reports; disease rates and trends; case-comparison (retrospective) studies; and cohort (prospective) studies. These methods cannot prove a causal relationship between exposure to a possible carcinogen and the occurrence of disease. Both the progestogen-only and the combined OC's protect against the development of benign breast disease, and there is no apparent association between OC use and the development of breast carcinoma. Long-term combined OC use appears to be related to the development of benign liver neoplasia, the risk increasing with steroid dose and age of the user. Long-term postmenopausal use of estrogens, but not progestogen-only or combined OC's, significantly increases the risk of developing endometrial hyperplasia and endometrial adenocarcinoma. The use of low-dose combined OC's does not appear to significantly increase the risk of leiomyoma, and there is no apparent increased risk of developing cervical dysplasia or carcinoma in situ among low-risk patients using low-dose combined OC's. High-risk patients taking high-dose OC's may be at increased risk for development of cervical dysplasia or progression to carcinoma in situ. Data are insufficient to establish any association between OC use and pituitary neoplasia, but OC's may have an adverse association with resolution of hydatidiform moles. (196 refs)

- 79-5443 Gastrointestinal Side Effects of Oral Contraceptives. (Ger) Braendli, B. (Gastroenterologische Abteilung Medizinische Klinik, Kantonsspital, CH-6004 Lucerne, Switzerland); Filippini, L. *Med Klin* 74(12): 425-436; 1979.

The use of oral contraceptives (OC) is associated with an increased incidence of liver neoplasms, usually benign. The most frequently occurring neoplasms have been termed liver cell adenoma, benign hepatoma, or focal nodular hyperplasia (FNH). Two recent studies differentiate between liver adenoma and FNH on pathological and angiographic grounds, and they state that the incidence of FNH is not related to use of OC. (157 refs)

- 79-5444 The Effects of Radiation on the Chromosomes of Patients Susceptible to Cancer. (Eng) Harnden, D. G. (Dept. Cancer Studies, Univ. Birmingham Medical Sch., Birmingham B15 2TJ, England); Taylor, A. M. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.: 52-61; 1978.

Evidence of radiosensitivity in patients with three genetically determined diseases, ataxia telangiectasia (AT), retinoblastoma, and basal cell nevus syndrome (BCNS), is reviewed. All three diseases are associated with an increased incidence of malignant disease, and the radiosensitivity may be directly linked to the primary susceptibility to cancer. The literature contains three case reports of AT patients with unusual radiosensitivity and several reports of severe responses to radiation therapy in BCNS patients. In addition, the osteosarcomas sometimes associated with retinoblastomas may be evidence of radiation sensitivity. A study of radiosensitivity at the cellular level showed a reduced survival of fibroblasts from AT patients when they were exposed to radiation. A recent report indicated an unusual radiosensitivity of cells from

a patient with retinoblastoma and an interstitial deletion of a chromosome 13 (most retinoblastoma patients have normal chromosomes). Cells from patients with BCNS display normal sensitivity to cell killing after exposure to γ -rays. Evidence of radiosensitivity at the chromosome level has been found only for AT, and various possible mechanisms leading to these chromosome aberrations are suggested. There is no definitive evidence that the radiosensitivity to chromosome damage in AT patients is linked to the observed spontaneous chromosome damage and clone formation or that the clones are in some way linked to a predisposition to lymphoid neoplasms. (47 refs)

- 79-5445 Regulation of Radiation Pollution: Its Possible Usefulness in Strategy for Intervention Against Chemical Mutagens. (Eng) Latarjet, R. (Section de Biologie, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex 5, France). *IARC Sci Publ* (25): 207-228; 1979.

The history of the regulation of radiation to limit human exposure is traced from the 1952 Conference on Radiobiology and Radiation Protection held in Stockholm to the present (1977). The present permissible radiation doses recommended by the International Commission for Radiation Protection (ICRP) are critically evaluated. The question is then raised as to whether the large volume of research in the field of radiation can serve as an example in regulation of chemicals. A system of rad-equivalences equating the biological effect of a 'dose' of a harmful chemical with that of a 'dose' of radiation is described. Once the equivalence is established experimentally, regulations concerning radiation safety can be extrapolated to apply to a given compound. The use of a common unit, the rad, would allow the summing of risks from several mutagens in order to determine a possible additive effect. Conditions necessary for establishing rad-equivalence are outlined; and ethylene, formaldehyde, and benzo(a)pyrene are given as examples. The limitations of the equivalence system are discussed; eg, each chemical may affect the DNA in a unique way to cause mutational changes. (29 refs)

- 79-5446 Aging, Environmental Influences, and Photocarcinogenesis. (Eng) Forbes, P. D. (Center Photobiology, Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Davies, R. E.; Urbach, F. *J Invest Dermatol* 73(1): 131-134; 1979.

Current understanding of aging, environmental influences, and photocarcinogenesis is reviewed. Many studies have provided evidence for the significance of light energy in the etiology of basal and squamous cell carcinomas. The induction of malignant melanoma may depend on the interaction of sunlight with other, as yet unidentified, factors. Several models for estimating the photobiological impact of the reduced ozone layer have been proposed. Because some of the variables in these models cannot be resolved with data from humans, the calculations must be based on studies of laboratory animals. Preliminary observations from such experiments and from limited clinical data suggest that the tumor response reflects two aspects of aging: the passage of time required by repeated exposure that results in accumulated damage and the biological effect correlated with time passage, ie, physiological age. The mechanism by which physiological age influences photocarcinogenesis is not clear. It may be based on a structural change (eg, thickening of the protective stratum corneum), a change in the biological properties of the organism (eg, a reduction in the DNA repair capacity or an alteration in the

fibrous protein), or any of the other phenomena currently associated with aging. (23 refs)

- 79-5447 Photochemotherapy in Psoriasis: A Review. (Eng) Vella Briffa, D. (Inst. Dermatology, St. John's Hosp. Diseases Skin, Homerton Grove, London E9 6BX, England); Warin, A. P. *J R Soc Med* 72(6): 440-446; 1979.

The use of photochemotherapy for psoriasis may be mutagenic or carcinogenic. In the presence of long-wave UV irradiation (UVA), psoralens produce mutagenic effects in various biological systems, and the ip or topical administration of 8-methoxypsoralen (8-MOP) followed by UVA exposure has been shown to initiate skin tumor formation in rodents. The only published evidence for the carcinogenicity of 8-MOP and UVA in humans comes from experiences with four xeroderma pigmentosum patients and one patient with vitiligo and a history of arsenic ingestion who developed multiple skin cancers within months of starting photochemotherapy. (94 refs)

- 79-5448 DNA Repair Processes Protect Human Beings from Premature Solar Skin Damage: Evidence from Studies on Xeroderma Pigmentosum. (Eng) Robbins, J. H. (NIH, Building 10, Room 12N238, Bethesda, MD 20014); Moshell, A. N. *J Invest Dermatol* 73(1): 102-107; 1979.

Studies of xeroderma pigmentosum (XP) are reviewed to elucidate mechanisms resulting in solar damage in normal persons. Histologically, hyperpigmented macules in XP patients, which occur on sun-damaged skin, may represent the spectrum of sunlight-induced melanocytic changes that can progress to malignant melanoma. Studies of defective UV light (UVL)-induced unscheduled DNA synthesis in XP cells, particularly in cell-fusion experiments, have been useful in the classification of XP patients into complementation groups. The atrophy of sun-exposed XP epidermis might reflect cellular sensitivity to the killing effects of UVL demonstrated in vitro. Fibroblasts from XP patients have a higher frequency per unit of UVL than normal fibroblasts. Such increased mutability of XP cells might be the basis for several of the clinical findings in the sun-exposed skin of XP patients. Mutation of dermal fibroblasts might result in abnormal metabolic processes that, perhaps, account in part for the basophilic degeneration of the collagen and for solar elastosis. (58 refs)

- 79-5449 Radiation-induced Sarcomas of Bone. (Eng) Brady, L. W. (Dept. Radiation Therapy and Nuclear Medicine, Hahnemann Medical Coll. and Hosp., 230 N. Broad St., Philadelphia, PA 19102). *Skeletal Radiol* 4(2): 72-78; 1979.

Data on radiation-induced bone sarcomas, the frequency of which is low, are reviewed. The radiobiologic effect of x- or γ -radiation is mostly determined by the magnitude of the absorbed dose and its distribution within the tissues. The wide variation in absorbed dose is most dramatic in patients treated with photon energies <500 kilovolts. There is wide disparity in absorbed dose between soft tissues and the immediately adjacent bone tissues. The more superficial portions of bone have higher dose distributions than the deeper surfaces. Most experiments on the production of tumors by irradiation have been concerned with carcinomas and superficial sarcomas. In humans, radiation osteitis is present in about 50% of the cases. The histologic features of bone tumors range from

osteogenic sarcomas in 50%-60% of the cases to fibrosarcomas, chondrosarcomas, aplastic spindle cell sarcomas, and giant cell carcinomas. The median latent period is 11 yr, and animal studies show that this period is inversely related to radiation dose. The radiobiologic mechanism in carcinogenesis at the dose level used in definitive radiotherapy is thought to be at least a product of two processes of cell kill probabilities and transformation rate. Cancerocidal levels leave fewer reproductively capable cells to proliferate in a transformed state. The literature shows that no radiation-induced sarcomas were seen at doses <3,000 rads given in 3 wk. Sensitivity to radiation carcinogenesis is thought to be related to the age of the patient. The induction of malignant bone tumors is so serious a late effect of radiation therapy that an estimate of the magnitude of the risk is important. With the changing contemporary management of malignant disease and with increasing numbers of patients being treated with combined radiation therapy and multiple drug chemotherapy, there may be an associated shortening of the cancer induction period and an increase in the frequency of second malignant lesions or neoplasms. Criteria for the diagnosis of radiation-induced bone sarcomas are presented. (53 refs)

- 79-5450 Evaluation of the Risks of Somatic Radiation and Recommendations of ICRP Publication No. 26 (1977). (Ger) Schmitz-Feuerhake, I. (Fachbereich Physik, Universität Bremen, Bibliothekstrasse, 2800 Bremen 33, W. Germany) Batjer, K.; Muschol, E. *ROEFO* 131(1): 84-89; 1979.

Data from several epidemiological studies of cancer incidence in population groups exposed to low levels of radiation were analyzed, as were the assumptions and calculations used to prepare the International Commission on Radiological Protection (ICRP) report No. 26. Data on cancer incidence among persons exposed to atomic bomb explosions, patients given radiation for benign conditions (spondylitis, tinea capitis), persons receiving above-average levels of natural radiation (eg, living at high elevations and along lines of geomagnetic flux), radiologists, and plutonium workers were analyzed to estimate cancer risk. The results showed that the risks from small doses of radiation were underestimated by a factor of approx 3 in the ICRP report. (64 refs)

- 79-5451 Is Ultrasonic Therapy Carcinogenic? (Eng) Wheeler, R. H. (Dept. Environmental, Public, and Occupational Health, American Medical Assoc., Chicago, IL). *JAMA* 242(2): 192; 1979.

Although ultrasound causes cavitation of cellular fluid, disruption in DNA strands, and acoustic microstreaming, there is no evidence that either acute or chronic ultrasonic radiation exposure induces tumors. (1 ref)

- 79-5452 Health Implications of Nuclear Energy (2 Letters to Editor). (Eng) Drum, D. E. (Harvard Medical Sch., Boston, MA 02115); Joseph, P. G. *Ann Intern Med* 91(1): 127-128; 1979.

A recent editorial on the potential health hazards of nuclear energy is discussed. It is stated on the one hand that there are no examples of known genetic effects caused by low-level (less than 5 roentgen-equivalents-man/yr) radiation in humans and that it has not been

proven that plutonium or spent fuel can cause high incidences of both prompt and latent cancer deaths. In contrast, strong support for the conclusion that nuclear energy poses significant health hazards is offered. (10 refs)

- 79-5453 Radioactivity in Nonuranium Mines and Its Effects on the Health of the Miners. (Rum) Mihail, G. (Institutul de igiena si sanatate publica, Iasi, Romania); Gradinaru, M.; Weissbuch, H. *Rev Ig [Bacteriol]* 27(4): 289-294; 1978.

The general occupational hygienic aspects of radiation from ^{222}Rn , ^{210}Pb , and ^{210}Po in nonuranium mines are reviewed. The carcinogenic effect of radiation can be enhanced by dust-induced lesions in the bronchial epithelium. (28 refs)

- 79-5454 The Specter of Malignancy and Criteria for Cell Lines as Substrates for Vaccines. (Eng) Salk, J. (Salk Inst. Biological Studies, P.O. Box 1809, San Diego, CA 92112). *Adv Exp Med Biol* 118: 107-113; 1979.

The factor limiting the acceptance of infinite life-span cell lines for vaccine production is the belief that vaccines made from viruses grown in these substrates might be oncogenic. If aneuploidy and infinite life-span are removed, the only criterion for exclusion would be tumorigenicity. It would be of value to carry out a systematic program to determine, in general, whether or not there are transmissible oncogenic factors in extracts of homologous tumorigenic cells or in vaccines made from noninfectious viruses propagated in them. (15 refs)

- 79-5455 Distinctive Mechanisms in Naturally Occurring Genetic Resistance to Leukemogenesis. (Eng) Steeves, R. A. (Albert Einstein Coll. Medicine, Bronx, NY); Moore, M. A.; Till, J. E.; Parkman, R.; Bennett, M.; Shearer, G. M.; Meruelo, D.; et al. In: *Natural Resistance Systems Against Foreign Cells, Tumours, and Microbes*. Proceedings of an International Conference held 18-22 October 1976, Jenner, CA. Cudkovic, G.; Landy, M.; Shearer, G. M., eds. (New York: Academic Press): 299 pp.; 197-232; 1978.

Genes that control resistance to Friend leukemia virus (FLV) in mice and studies of T suppressor cells and Hh effects are reviewed. The Fv-1 gene is dominant for resistance, with the n and b alleles conferring resistance to murine leukemia virus of the opposite tropism. This resistance is directed against the helper virus in FLV stocks rather than against the virus directly responsible for spleen focus formation. The Fv-2 gene is recessive for resistance to FLV and presents spleen focus formation after FLV infection. The Fv-2 gene may be demonstrable in uninfected mice and may affect an essential step in embryogenesis. In in vitro cultures of bone marrow from resistant C57BL/6 mice, resistance is demonstrated in terms of leukemic transformation and resistance with respect to propagation of the FLV complex. Mitogen-responsive cells are resistant to FLV, but they are the targets of T suppressor cells. The latter are activated by FLV to suppress the former, and the numbers and/or functions of the suppressors are regulated by M cells. An interfering cell interacts with the H-2D gene product of the mitogen-responsive cells, and H-2D incompatibility between the interfering and mitogen-responsive cells prevents T suppressors from functioning. Susceptibility or resistance in vitro is not linked

REVIEW

with Fv-2. A restricted suppressor cell in AKR leukemia functions via cell contact; the features of this cell are described. The suppressors are Thy-1-positive. Studies are summarized that indicate that certain tumor cells express Hh antigen on their surface. Hybrid resistance to bone marrow transplantation appears to be a manifestation of lymphoma resistance. Gene(s) regulating cell-mediated lymphocytotoxicity responsiveness to AKR tumor cells have been tentatively mapped to the I-J subregion. The targets involved in marrow rejection and graft-vs-host reactions are discussed. (no refs)

- 79-5456 **The Physiopathology of Friend Leukemia.** (Eng) Tambourin, P. E. (Unité de Physiologie Cellulaire INSERM, Unit 22, Institut Curie, Batiment 110, Faculté Paris-Sud, 91405 Orsay, France); Wendling, F.; Jasmin, C.; Smadja-Joffe, F. *Leuk Res* 3(3): 117-129; 1979.

The physiopathology of Friend and Rauscher leukemias (FL and RL), which appear to be multiple-step, virus-induced malignant diseases, is reviewed. The sequence of events in the course of these leukemias is remarkably reproducible. Early events occur as soon as 30 hr after virus infection and result in the massive appearance of hyperbasophilic cells, mainly in the spleen. These cells, which look like proerythroblasts, undergo a pathological erythropoietic differentiation without erythropoietin. They derive from the morphological transformation of erythropoietin-responsive cells or closely related precursors. This initial phase can be characterized as a malignant compartmental disorganization: pathological erythroid cells have a finite life-span, but the size of the compartment of erythroid precursors is uncontrolled, and its inflation leads to the death of leukemic mice. A second step, characterized by the emergence of truly malignant cells, takes place much later. The characteristics of the pre- and neoplastic cell populations that result from these two major steps suggest that they are probably related to each other. In contrast to spontaneous or chemically induced carcinogenesis the multiple-step model is rare in viral oncogenesis. However, it cannot be excluded that this is in fact the case for most virus-induced leukemias. The FL process may provide a unique model for the study of the transforming event itself (leading to the appearance of pathological cells with a definite life span) and the sequence of events involved in the outgrowth of tumor cells. (104 refs)

- 79-5457 **Role of Hepatitis B Virus in Primary Liver Cancer.** (Eng) Zuckerman, A. J. (Dept. Medical Microbiology, London Sch. Hygiene and Tropical Medicine, Univ. London, London, England). *J Toxicol Environ Health* 5(2/3): 275-280; 1979.

The role of hepatitis B virus (HBV) in the etiology of primary hepatocellular carcinoma is reviewed. There is an excess prevalence of markers of active infection with HBV in patients with primary liver cancer in many parts of the world. Early age of infection with HBV is likely to be an important factor, resulting in persistent infection that may progress to chronic liver damage. Results of recent experimental studies are consistent with the integration of HBV DNA with host cell DNA molecules. It is likely that primary liver cancer is the cumulative result of several cofactors, including infection with HBV; genetic, immunologic, hormonal, and nutritional factors; and environmental factors, including mycotoxins and chemical carcinogens. (18 refs)

- 79-5458 **Mammary Tumor Viruses.** (Eng) Moore, D. H. (Dept. Microbiology and Immunology, Hahnemann Medical Coll. and Hosp., Philadelphia, PA); Long, C. A.; Vaidya, A. B.; Sheffield, J. B.; Dion, A. S.; Lasfargues, E. Y. *Adv Cancer Res* 29: 347-418; 1979.

An extensive review is presented of mammary tumor viruses (MTV). The topics covered include the morphology of MTV, structural proteins and RNA-directed DNA polymerase of murine MTV (MuMTV), synthesis and assembly of MuMTV proteins, genome of MuMTV, in vivo infection and tumorigenesis of MuMTV, infectivity of endogenous MuMTV, dependence of MuMTV infectivity on mouse strain, transmission of MuMTV by contact, in vitro infection of cells by MuMTV, techniques for and results of antigenic characterization of MuMTV and its components, humoral and cellular immune responses of the host to MuMTV, modulation of the immunologic interaction between MuMTV and its host, and the possibility of an MuMTV-related virus in humans. (279 refs)

- 79-5459 **Introduction--Heterogeneity of the Cellular Immune Response.** (Eng) Dvorak, H. F. (Dept. Pathology, Massachusetts General Hosp., Boston, MA). *Adv Exp Med Biol* 114: 369-374; 1979.

The relevance of nonlymphoid cells in immune reactions is reviewed. When sensitized guinea pigs were injected ip with line 1 or line 10 tumor cells, the principal finding 1-3 days later was variably sized aggregates of inflammatory and damaged or dying tumor cells. Injection of tumor cells into the skin of sensitized animals without BCG led to a reaction involving extensive local infiltrations of basophils (which accounted for 12%-23% of the total inflammatory cells). Frequent intimate associations between infiltrating basophils and viable and necrotic tumor cells were observed. Within hours after injection of line 1 cells into the sc space of unsensitized guinea pigs, the tumor cells formed clumps and became invested in a semirigid, fibrin-gel cocoon. This mass became vascularized by day 3 and was subsequently replaced by fibrous connective tissue. Beginning at about day 8, there was evidence of developing cellular immunity. The tumor cells showed progressive evidence of damage during this period, culminating in widespread tumor death. Tumor cell injury and necrosis were preceded by and correlated with substantial and widespread microvascular compaction and damage to the endothelium of the small vessels supplying the tumor cells and the surrounding connective tissue. The pattern of necrosis had many characteristics of ischemia progressing to infarction, and the microvascular changes observed may have had an immunological basis. The data indicate that the response of the host to the same inoculum of tumor cells varies enormously, depending on the immune status of the host and the site of injection. (19 refs)

- 79-5460 **NK Cell Systems as Effectors of Resistance to Normal and Malignant Hemopoietic Cells.** (Eng) Wigzell, H. (Univ. Uppsala, Uppsala, Sweden); Cudkovicz, G.; Elkins, W. L.; Boranic, M.; Henney, C. S.; Sprent, J.; Festenstein, H.; et al. In: *Natural Resistance Systems Against Foreign Cells, Tumors, and Microbes*. Proceedings of an International Conference held 18-22 October 1976, Jenner, CA. Cudkovicz, G.; Landy, M.; Shearer, G. M., eds. (New York: Academic Press): 299 pp.; 173-196; 1978.

The relationship of natural killer (NK) cells in rats and mice to

marrow and leukemia resistance is reviewed. The initiation of lysis by NK cells is extremely rapid, indicating that there is some kind of induction of a cytolytic capacity via in vitro contact with target cells. The NK cell functions as though its lytic ability were mediated via receptors it produces itself. A considerable variation in target cell sensitivity is evident in various kinds of NK cell systems. There is no indication that the receptors on NK cells are related to conventional immunoglobulins. There is a direct correlation between NK cell activity as measured in vitro and the ability to passively transfer protection against Moloney lymphomas. NK activity is transferred by fetal liver irrespective of the host genotype. There is no indication as to the exact nature of the target structures or what determines sensitivity, although sensitive targets have been found only among hematopoietic cells. Antiserum against Ly1.2 appears to selectively eliminate NK cells from a heterogeneous lymphocyte population. In an irradiated animal, NK cells return within 3 wk after transplantation of bone marrow cells. It is possible that the NK cell is in the granulocytic lineage, perhaps at an early stage of differentiation, although there are arguments against this view. Both NK and T cells could play important roles in surveillance against tumors, perhaps responding to different types of stimuli. A macrophage-type cell can markedly suppress the activity of NK cells in the cytotoxicity assay. The NK cell, resistance to bone marrow transplantation, and resistance to leukemia are intimately related. However, there is no evidence that the same cell is responsible for all three phenomena. (no refs)

- 79-5461 Macrophages and Immunity: Mechanisms and Effects of Macrophage Activation. (Fre) Dumont, A. (Faculte de Medecine, Departement de Pathologie, Universite de Montreal, Montreal, P.Q. H3C 3J7, Canada). *Union Med Can* 108(6): 705-710; 1979.

Recent experimental work defining the nature and role of the macrophage in immune reactions is reviewed. Evidence obtained in in vivo and in vitro studies shows that activated macrophages have cytostatic and/or cytolytic effects on tumor cells. Various substances, including (polyanionic compounds, endotoxins, and lipopolysaccharides, can activate macrophages. The substances released by macrophages that cause cytostasis or cytolysis are thought to be hydrolytic enzymes. The role of complement and lymphokines in the cytostatic and cytolytic activity of macrophages is discussed. At this time, none of the animal studies of macrophage antitumor activities have been verified in humans. (14 refs)

- 79-5462 Thymic Functions and Resistance to Foreign Hemopoietic Grafts. (Eng) Stutman, O. (Memorial Sloan-Kettering Cancer Center, New York, NY); Warner, N. L.; Elkins, W. L.; Cudkowicz, G.; Sprent, J.; Golub, E. S.; Bennett, M.; et al. In: *Natural Resistance Systems Against Foreign Cells, Tumors, and Microbes*. Proceedings of an International Conference held 18-22 October 1976, Jenner, CA. Cudkowicz, G.; Landy, M.; Shearer, G. M., eds. (New York: Academic Press): 299 pp.; 31-45; 1978.

The restoration, by grafting, of T-cell function in athymic recipients is reviewed. In contrast to syngeneic thymus grafts, allogeneic grafts produce poor immunological restoration of neonatally thymectomized mice, and the allogeneic grafts are not repopulated and only rarely acquire the appearance of a normal thymus. In unirradiated recipients, there appears to be strict histocompatibility restrictions between the thymus and migrating

hematopoietic cells. When an F₁ thymus is grafted into parental strains, tolerance induction to skin of the same origin is dependent on the strain combination used. Graft-vs-host (GVH) reactivity is a restricted event. There is no evidence of Hh gene expression on thymus cells. Data support the idea that genetic resistance is exerted upon T- and B-lymphocyte clones. In the thymus there are two sets of cells: cortisone-sensitive and nonfunctional and one cortisone-resistant and functional in the periphery. The role of the cortisone-resistant cells within the thymus is unknown. T cells are not involved in anti-Hh responses in vivo, marrow graft rejection being stronger in the absence of these cells. However, in vitro, where the end point is lysis rather than cytoablation, the effectors of the F₁ and antiparent responses are Thy-1 positive cells. (no refs)

- 79-5463 Natural Resistance to Foreign Hemopoietic and Leukemia Grafts. (Eng) Cudkowicz, G. (State Univ. New York at Buffalo, Buffalo, NY); Sanford, B. H.; Van Bekkum, D. W.; Bach, F. H.; Storb, R.; Warner, N. L.; Moore, M. A.; et al. In: *Natural Resistance Systems Against Foreign Cells, Tumors, and Microbes*. Proceedings of an International Conference held 18-22 October 1976, Jenner, CA. Cudkowicz, G.; Landy, M.; Shearer, G. M., eds. (New York: Academic Press): 299 pp.; 1-30; 1978.

The features that distinguish bone marrow transplants from other types of grafts are reviewed. By integrating data obtained in vitro and in vivo, a comprehensive model for natural resistance to normal and malignant hematopoietic grafts was derived. Central to all manifestations of such anti-Hh (anti-hematopoietic histocompatibility) reactions is a macrophagelike cell that interacts in vivo with the effectors (or their precursors) of resistance. These in vivo effectors are conspicuous with respect to their lack of T-cell markers and their low sensitivity to radiation. They are viewed as subpopulations differing essentially in the target cell structure they recognize, ie, in their specificity. In vitro, the same central macrophagelike cell interacts with T cells in the generation of F₁ antiparent cytotoxicity. The genetic control operates at two levels. The H-2 region may be involved in determining the nature or expression of the Hh antigens, and it also may be involved in controlling the immune response to various cell-surface antigens. The data presented and a proposed model are discussed by a panel. (no refs)

- 79-5464 Observations on Immunology and Oncology of Paraproteins. (Ger) Mey, U. (Med. klinik der Med. Akademie, Leipziger Strasse 44, DDR-20 Magdeburg, E. Germany). *Z Gesamte Inn Med* 34(7): 182-185; 1979.

Paraproteins (M proteins: M-PT's) were long considered abnormal proteins not found in normal human plasma. Recently, amino acid analyses have shown that M-PT's have the same structure as some immunoglobulins; in some diseases, a cell clone produces abnormally large amounts of M-PT. Fragments of M-PT, designated heavy and light chains, are also found in these diseases. M-PT's are found not only in classic monoclonal gammopathies, but also in Hodgkin's disease and autoimmune diseases (ulcerative colitis, Crohn's disease). A hypothesis based on results in mice suggests that all lymphomas, including those of humans, result from the activation of a resting oncogenic virus and, thus, a disturbance in the lymphatic cell system. The M-PT would then be a product of tumor virus information incorporated into the genomes of B lymphocytes. The functional characteristics of M-PT's (lymphocytotoxicity, aggregation, binding to blood cells) lead to the

REVIEW

clinical symptoms of M-PT diseases (immune defects, nephropathy, amyloidosis, hemorrhagic diathesis). If these changes in protein structure are caused by an oncogenic virus, benign paraproteinemia would not exist; however, some of the diseases could be classified as having a relatively benign course. (78 refs)

- 79-5465 α -Fetoprotein in Cancer and Fetal Development. (Eng) Ruoslahti, E. (Div. Immunology, City Hope Natl. Medical Center, Duarte, CA); Seppala, M. *Adv Cancer Res* 29: 275-346; 1979.

Data on the occurrence of α -fetoprotein (AFP) in cancer and fetal development are reviewed. The topics included are antibodies to AFP, interspecies cross-reactions, immunological cross-reactions between AFP and albumin, immunoassays of AFP in biological fluids, international standard for AFP, detection of AFP synthesis by internal labeling, detection of AFP in tissues, sites of physiological AFP synthesis, physiological concentrations of AFP in body fluids, biological half-life of AFP, purification of AFP, physical and chemical properties of AFP, possible immunoregulatory role for AFP, AFP in liver injury and hepatocarcinogenesis, AFP in germ cell tumors, and the use of AFP levels in the diagnosis of liver diseases, trophoblastic disease, and fetal pathology. (318 refs)

- 79-5466 Biochemical Strategy of Hepatomas. (Eng) Weber, G. (Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianapolis, IN); Kizaki, H.; Shiotani, T.; Tzeng, D.; Williams, J. C. *J Toxicol Environ Health* 5(2/3): 371-386; 1979.

The enzymology and metabolism of hepatomas is discussed in terms of the pattern that reveals the biochemical strategy of the cancer cells. Particular emphasis is placed on aspects of pyrimidine biosynthesis. Included in the discussion are the molecular correlation concept; transformation-linked alterations and progressions in biochemical strategy; evidence for reprogramming of gene expression, such as alterations in enzyme concentration and isozyme pattern; the 'key enzyme' concept; and biological model systems. The linking of enzymatic and biochemical markers with malignant transformation and progression includes reciprocal regulation, a pattern of metabolic imbalance in purine metabolism, imbalance in pyrimidine and DNA metabolism, and enzymatic imbalance in cytidine 5'-triphosphate biosynthesis in hepatomas. The applicability of biochemical imbalance discovered in rat hepatomas to other types of tumors in rodents and in humans, and the biochemical strategy of human hepatomas are considered. It is demonstrated that the biochemical strategy first identified in a series of transplantable rat hepatomas is applicable to human primary hepatomas. (35 refs)

- 79-5467 Antigenic Changes Associated with Liver Carcinogenesis. (Eng) Embleton, M. J. (Cancer Res. Campaign Labs., Univ. Nottingham, University Park, Nottingham, England). *J Toxicol Environ Health* 5(2/3): 453-468; 1979.

Cells undergoing neoplastic transformation after treatment with chemical carcinogens often express antigens that are not expressed in their normal counterparts in adult hosts. These individually

distinct antigens are capable of inducing tumor immunity in syngeneic hosts. They arise as a consequence of cell-carcinogen interaction, and they may result from the modification or replacement of normal cell-surface components. Their role in immunosurveillance is not established, but they offer a target for tumor immunotherapy. Reexpressed fetal antigens have also been detected, either as secretory products (α_1 -fetoprotein) or as common cell-surface components, on hepatoma cells. These antigens may be important diagnostic indicators of neoplastic change. Common antigens initiated early after carcinogen treatment, before malignant cells are detected, are possibly associated with the fetal antigens. Together, the antigens associated with liver carcinogenesis may prove to be powerful tools in understanding the process of liver neoplasia. (68 refs)

- 79-5468 Anorexia Pancreatica. (Rus) Vasilenko, B. Kh. (No affiliation given). *Klin Med (Mosk)* 57(6): 19-21; 1979.

Difficulties encountered in the early diagnosis of pancreatic cancer are reviewed briefly. The initial complaints include epigastric or back pain (approx 50% of the patients) and jaundice (25%-30%). The most important symptom was found to be a complete loss of appetite (anorexia pancreatica). It was suggested that the anorexia is caused by a severe inhibition of the alimentary canal. (no refs)

- 79-5469 Use of Nude Mice for Studies on the Tumorigenicity of Animal Cells. (Eng) Freedman, V. H. (Dept. Genetics, Albert Einstein Coll. Medicine, Yeshiva Univ., Bronx, NY); Shin, S. In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 353-384; 1978.

The use of the nude mouse as a means of determining the tumorigenicity and tumor growth patterns of animal cells is reviewed. In most cases, the nude mouse is immunologically oblivious to the injected cells, so that the formation of tumors can be attributed solely to intrinsic cell properties. Established cell lines and virally transformed cells able to proliferate without anchorage in vitro are capable of generating tumors in nude mice. When nontumorigenic cells are passaged in semisolid medium, clones showing anchorage independence also show an ability to form tumors in nude mice. Passage of poorly tumorigenic cells through methylcellulose leads to an enrichment of anchorage-independent cells with greatly enhanced tumorigenicity. Thus, there appears to be an intimate and specific relationship between the anchorage-independent phenotype in vitro and the ability of a cell to generate tumors in the nude mouse. Several structural and functional parameters have been associated with tumorigenic potential in the nude mouse; eg, actin cables in the cytoplasm and the synthesis and secretion of plasminogen activator. In general, host cell transformation and recruitment are not involved in tumor growth, and the absence of induction of host-specific endogenous viruses or tumor cell-specific latent viruses during tumor growth was demonstrated in at least one instance. Cell-specific biochemical, chromosomal, and antigenic markers are not demonstrably altered during tumor growth, and there is extensive evidence that tumors that develop in nude mice after implantation of heterologous malignant tumor retain the original tumor histopathology. (36 refs)

- 79-5470 The Growth Behavior of Virus-transformed Cells in Nude Mice. (Eng) Stiles, C. D. (Dept. Microbiology and Molecular Genetics, Harvard Medical Sch., Boston, MA); Kawahara, A. A. In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 385-409; 1978.

The tumorigenic behavior of cell cultures derived from normal and neoplastic tissues in nude mice is reviewed, as is the available data on the tumorigenic behavior of viral-transformed cells in nude mice. Tumorigenicity of animal and human cell cultures in athymic nude mice is generally a reliable indicator of neoplastic potential. Under conditions in which most cell lines derived from human tumors are tumorigenic in nude mice, most human fibroblast and lymphocyte cultures transformed by DNA viruses are not tumorigenic. However, cell cultures that fail to form tumors in nude mice cannot automatically be described as "normal". The integration of DNA virus genetic material is insufficient for malignant behavior in vivo. There is some evidence that the integration of RNA tumor virus genomes is sufficient for neoplastic behavior, but the data are too scanty for generalizations to be made. Of the in vitro criteria that define the transformed state, there is no single parameter that is a sufficient indicator of tumorigenic potential in nude mice. Studies of the tumorigenicity of virus-transformed cells in nude mice may shed light on the physiological nature of growth-regulatory signals and clarify the extent to which individual virus species constitute an oncogenic threat to humans. (42 refs)

- 79-5471 Spontaneous, Viral, and Chemically Induced Tumors in the Nude Mouse. (Eng) Stutman, O. (Memorial Sloan-Kettering Cancer Center, New York, NY). In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 411-435; 1978.

The growth of spontaneous and of virally and chemically induced tumors in the nude mouse is reviewed. Previous investigators have reported an absence of tumors in nude mice or, conversely, an inordinately high incidence of lymphomas in these animals. However, controlled experiments indicate that the incidence and types of spontaneous tumors in nude mice are basically comparable to those in immunologically normal control mice. Both the tumor incidence and type in nude mice follow those in the inbred strain from which the nude animals are derived. There is more general agreement on the oncogenic effects of DNA and RNA oncogenic viruses in nude mice. Nude mice partially inbred to various background strains showed increased susceptibilities to tumor induction with polyoma viruses. Similar studies showed that nude mice can, under certain circumstances, develop alternative immune responses that can act as surveillance devices. Both nude and normal control mice developed a 100% incidence of tumors following infection with Moloney sarcoma virus, but regressions were observed only in the normal animals. Thus, the thymus dependence of tumor regression is unquestionable. The focus-forming component of Friend leukemia virus can be detected in nude mice infected with this virus. The actual tumor incidence and latency periods for tumor development in nude mice and their immunologically normal controls are generally comparable following treatment with chemical carcinogens. In general, the data indicate that there is no clear correlation between the immune deficiency of nude mice and any form of peculiar risk for tumor development. (47 refs)

- 79-5472 Transplantation of Heterologous Endocrine Tumor Cells in Nude Mice. (Eng) Reid, L. C. (Dept. Biology,

Muir Coll., Univ. California at San Diego, La Jolla, CA); Shin, S. In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 313-351; 1978.

The transplantation of heterologous endocrine tumor cells in nude mice is reviewed. Many transplantable lines derived from hormone-secreting and -dependent tumors have been established in nude mice. All tissues, whether normal, benign, or malignant, may survive indefinitely when implanted in nude mice, although benign tumors eventually cease growing. There is a variably long "adaptation period" for the transplanted tumor in the first passages; the ability to vascularize appears to be one of the important factors in this variability. The tumor lines established in nude mice usually retain their morphological and biochemical differentiation through serial transplantation. However, the tumors show a gradual enrichment for the fastest growing tumorigenic cells with a gradual elimination of the normal and benign components in the original specimen. Not all heterologous specimens will produce tumors in nude mice, and the site of implantation may be an important factor for growth. The development of transplantable endocrine tumor lines from functional tumors may be prevented if the tumors secrete lethal amounts of a hormone, unless the transplant recipient can be "preconditioned" by surgery, etc, so that the lethal effect can be circumvented. The transplantable tumor lines maintained in nude mice are expected to provide model systems for studies of hormone synthesis and secretion, determination of hormone requirements for the growth of specific endocrine cells, and for the purification of new hormones. (36 refs)

- 79-5473 Cellular Differentiation, a Problem in Oncology. (Por) Silvany, A. M. (Departamento Histologia e Embriologia, Fac. Med. Univ. Federal da Bahia, Bahia, Brazil). *Rev Bras Cancerol* 28(4): 61-73; 1978.

Data on the process of differentiation are reviewed, particularly studies at the molecular level. Differentiation is due to selective gene-regulation mechanisms, and cancer could result from aberrant gene regulation. Metaplasia and the histologic grading of malignant tumors are also reviewed. (35 refs)

- 79-5474 The Role of Inheritance in Malignant Disease. (Ger) Muller, H. (Abteilung Genetik, Universitäts-Kinderklinik, Romergasse 8, CH-4005 Basel, Switzerland). *ZFA (Stuttgart)* 55: 917-923; 1979.

Studies of genetic factors involved in cancer development show that individual differences in response to carcinogens (viruses, chemicals, and ionizing radiation) are due to the genetic factors. On the other hand, the cancer risk of familially predisposed subjects is also influenced by environmental factors. (10 refs)

- 79-5475 Development of a Neonatal and Metastatic Murine Neuroblastoma Model (2 Letters to Editor). (Eng) Lueker, D. C. (Dept. Microbiology, Colorado State Univ., Fort Collins, CO 80523); Stewart, I. B.; Kainer, R. A.; Schengrund, C. L.; Repman, M. A.; Sheffler, B. A. *Cancer Res* 39(8): 3277-3278; 1979.

Conflicting findings obtained in two studies of a neonatal and metastatic murine neuroblastoma model are discussed. In the first

study, mice inoculated sc with 5×10^5 cells did not develop metastasis, but metastasis did occur when 2×10^5 cells were injected id. In the second study, metastases were observed when the mice were inoculated sc. Also, in contrast with the first study, reduced mortality was observed when the same number of tumor cells were injected id. However, the contrasting results could be due to a difference in the neuroblastoma lines used: a cloned line was used in the first study and an uncloned C-1300 neuroblastoma was used in the second. Cloning may select for certain characteristics that may or may not alter the in vivo behavior of the cells. (6 refs)

- 79-5476 Role of Genetic Disorders in Retinoblastoma. (Pol) Sporny, S. (Zaklad Anatomii Patologicznej, Instytut Patologii AM, ul. Narutowicza 96, 90-139 Lodz, Poland); Pruszczyński, M. *Pol Tyg Lek* 34(3): 107-109; 1979.

Studies of retinoblastoma and its relationship to genetic disorders are reviewed. Retinoblastoma has been found to be associated with trisomy 21, tetrasomy (48, XXX, G+ or 48, XXY, G+), or ring chromosome 13 (46, XX, Dr or 46, XY, Dr). (24 refs)

- 79-5477 Tumors of the Eyeball. (Ger) Fanta, H. (Augenabteilung der Krankenanstalt Rudolfstiftung, Ferstelgasse 4, A-1090 Vienna, Austria). *Klin Monatsbl Augenheilkd* 174(3): 411-420; 1979.

After a classification of tumors of the eyeball as benign vs malignant or pigmented vs nonpigmented, attention is drawn to the fact that most of these tumors lie in the palpebral fissure and are benign. Leukoplakia is a clinical description but not a diagnosis. Leukoplakia can be used to describe both benign and malignant growths. Intraepithelial epithelioma is often incorrectly diagnosed as Bowen's disease. This disease of the skin and intraepithelial epithelioma of the limbus are histologically quite different, and, therefore, the term Bowen's disease is incorrect. Not all the various tumors occur with the same incidence; eg, squamous cell carcinoma occurs more often in some countries than in others. Malignant melanomas of the conjunctiva are not as malignant as those of the caruncle or cornea. In the conjunctiva, secondary melanomas can occur after penetration of an intraocular melanoma through the sclera; similarly, metastases can occur in the form of epibulbar tumors. In all cases, the epibulbar tumor should be excised carefully. A histological examination is necessary for diagnosis. (19 refs)

- 79-5478 Neck Mass of Uncertain Etiology. (Eng) Clairmont, A. A. (Dept. Surgery, Emory Univ. Sch. Medicine, Atlanta, GA); Richardson, G. S. *Pennsylvania Med* 82(8): 29-31; 1979.

A systematic diagnostic approach to the patient with a neck mass of uncertain etiology is reviewed. Ninety percent of all isolated neck masses in adults are metastatic carcinomas, and 90% of these are metastatic from primaries above the clavicle. However, involved supraclavicular nodes usually have a primary site below the clavicle. Approx 40% of the primary head and neck lesions in adults involve the laryngopharynx, 40% involve the oropharynx, and 10% involve the thyroid. In children, carcinoma accounts for only approx 33%-60% of malignant disease. In children, masses

occurring in the posterior triangle, unilateral node enlargement, or the presence of a node larger than adjacent lymphoid structures are causes for concern. In the adult, the location suggests a different approach to diagnosis of the etiology. The search for the primary lesion may involve laboratory studies, roentgenologic studies, panendoscopy, and needle aspiration biopsy of the mass. The excisional biopsy should be followed by definitive surgery and, possibly, radical neck dissection. The need for close follow-up examinations of all patients with occult primary lesions is stressed. (13 refs)

- 79-5479 Anatomical Features of the Origin and Spread of Tumours. (Eng) Levene, A. L. (Dept. Histopathology, Royal Marsden Hosp., London, England). *Ann R Coll Surg Engl* 60(1): 28-35; 1978.

The part played by anatomical factors in determining variations in the origin, distribution, shape, and mode of spread of different tumors is discussed, and the need for surgeons to bear these factors in mind in diagnosis and treatment is emphasized. Tables listing sites of predilection for bone tumors, the anatomical distribution of some nonepithelial neoplasms, and sarcomas that metastasize to lymph nodes in a significant proportion of cases are presented. (10 refs)

- 79-5480 Birthmarks: II. Melanocytic and Epidermal Nevi. (Eng) Jacobs, A. H. (Dept. Dermatology, Stanford Univ. Sch. Medicine, Stanford, CA). *Pediatrics* 1(2): PIR47-PIR50; 1979.

Data on melanocytic and epidermal nevi are reviewed. The acquired melanocytic nevi usually develop between the second and sixth year and may appear in crops at puberty. The individual risk of eventual malignant transformation is only about 1/1,000,000. The location and histologic type of the nevus are not related to the likelihood of such transformation. A truly congenital nevus should have its history dating to the actual time of birth. The incidence of malignant melanoma arising in these nevi may approach 10%, and 60% of the melanomas that have occurred in congenital nevi have done so during the first decade of life. Cafe-au-lait spots are usually present at birth or they appear in early childhood. When six or more spots are present, especially if they are ≥ 1.5 cm in diameter, there is a strong possibility that the patient has, or will develop, neurofibromatosis. Cafe-au-lait spots are also associated with tuberous sclerosis, pulmonary stenosis, and temporal lobe dysrhythmias. The most common epidermal nevi are the verrucous nevus and sebaceous nevus. Both are either congenital or appear within the first year. Total surgical excision is the treatment of choice for sebaceous nevi, since basal cell carcinoma may eventually develop during middle life. The epidermal nevus syndrome is one in which an extensive epidermal and/or sebaceous nevus is associated with multiple skeletal and neurologic abnormalities. (8 refs)

- 79-5481 Amyloid Disease. General Review. (Fre) Vincent, J. P. (Hopital Louis Mourier, F 92701 Colombes Cedex, France); Hardouin, J. P.; Devars Du Mayne, J. F. *Rev Fr Gastroenterol* (149): 47-50, 53; 1979.

The histological diagnosis of amyloid disease based on identification of the infiltration of organs with amyloid substance (AS) is reviewed. The different types of amyloid disease include primary

hereditary amyloid disease of endocrine tumors or APUD (amine precursor uptake and decarboxylation) amyloidosis, senile amyloid disease, and amyloid disease secondary to other diseases, such as cancer. Amyloidosis can be a complication of Hodgkin's disease, chronic lymphoid leukemia, and, less frequently, cancer of the viscera. Tumors of the APUD system secrete a substance that takes up histological stains in a manner similar to that of AS but differs from AS biochemically. The relationship between AS and immunoglobulins is discussed. Animal experiments show that prolonged immunological stimulation can result in amyloid disease. In the induction phase of amyloid disease in animals, there is an increase in plasma α_2 -globulins and γ -globulins and a proliferation of reticuloendothelial cells. (9 refs)

- 79-5482 Kupffer Cell Suspensions and Cultures as a Tool in Experimental Carcinogenesis.** (Eng) Munthe-Kaas, A. C. (Dept. Pathology, Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Montebello, Oslo, Norway). *J Toxicol Environ Health* 5(2/3): 565-573; 1979.

The interactions of Kupffer cells, phagocytes lining the sinusoids, and hepatocarcinogens are reviewed. Environmental carcinogens must first traverse a Kupffer cell barrier before reaching the liver parenchyma. Phagocytosis and subsequent degradation of carcinogens by Kupffer cells lead to their permanent removal. Factors such as membrane receptors, which determine the avidity of Kupffer cells for various substances, would consequently have a decisive role in the primary interaction between carcinogens and Kupffer cells. Likewise, the intracellular lysosomal apparatus, which determines the ability of these cells to degrade various substances, would determine whether these substances can persist in an active form. In vivo data on Kupffer cell clearance of various substances are plentiful. However, to dissect the complex problem of Kupffer cell interaction with carcinogens, a clear-cut in vitro system would be useful. A system for separating Kupffer cells from other types of liver cells and maintaining pure Kupffer cell cultures has been achieved in recent years. Some basic cell biology studies, such as studies of membrane receptors and lysosomal enzyme apparatus, have already been made. (57 refs)

- 79-5483 Gut Endocrine Tumour Syndromes.** (Eng) Holst, J. J. (Inst. Medical Physiology C, Univ. Copenhagen, Copenhagen, Denmark). *Clin Endocrinol Metab* 8(2): 413-432; 1979.

Gastrointestinal tract endocrine tumor syndromes except for carcinoid tumors and the Zollinger-Ellison syndrome, are reviewed with emphasis on advances of clinical relevance. In recent years, a number of new cells have been characterized, and peptides that were originally found in nervous tissue have been localized to endocrine cells in the gastroenteropancreatic system. Nothing is known about the etiology of the gastrointestinal tract endocrine tumors, although inheritance may play a role in some instances. A ductular origin is suspected for most of the pancreatic tumors. The following main syndromes are discussed: the Verner-Morrison syndrome; the insulinomas; the glucagonoma syndrome; stomatostatinoma; and multiple endocrine adenopathy. The diagnosis of a gut endocrine tumor often rests on the demonstration of hypersecretion of the gastrointestinal peptides. Since these measurements do not necessarily reveal the site of hypersecretion, however, localization procedures such as selective angiography, ultrasound and computed tomography, and selective venous sampling are important. (89 refs)

- 79-5484 Carcinoma of the Gastric Stump.** (Ger) Luders, K. (Chirurgische Klinik, Nordwestkrankenhaus, Steinbacher Hohl 2-26, D-6000 Frankfurt/Main 90, W. Germany); Radomsky, J.; Ungeheuer, E. *Med Klin* 74(14): 91-100; 1979.

The epidemiology and diagnosis of carcinoma of the gastric stump (GSC) are reviewed. This lesion is defined as a carcinoma found in the gastric remnant at least 5 yr after surgical removal of part of the stomach because of benign disease. The age distribution and histology of GSC are similar to those of primary gastric carcinoma (PGC). Many studies have established a two- to fourfold increased risk of carcinoma in subjects who have undergone gastric resection compared with that in the general population. The risk of GSC seems to be greater for patients whose surgery was for peptic ulcers than for those whose surgery was for duodenal ulcers. Epithelial irritation from jejunal reflux and chronic atrophic gastritis with anacidity are suggested causes of the increased risk. The av interval between surgery and GSC is 20-25 yr; the intervals tend to be longer in younger patients ($p < 0.001$). The av time between first symptoms and correct diagnosis was 10 mo for 14 patients with GSC, vs 4.6 mo for those with PGC. Symptoms (wt loss, pressure or pain in the stomach, belching, vomiting) are usually not noted until the GSC is advanced. Endoscopy should be done yearly on patients with gastric remnants up to age 60, and then twice a year, even if they are symptom-free. In GSC patients, the surgical mortality is higher and the survival time is lower than those in PGC patients. (43 refs)

- 79-5485 The Association Between Diabetes Mellitus and Endometrial Carcinoma.** (Ger) Dillinger, P. (Klinikum rechts der Isar, Technische Universität München, Munich, W. Germany); Koeppe, H. W. *Med Klin* 74(8): 284-287; 1979.

A positive association between diabetes mellitus and endometrial carcinoma has been observed in several studies. The hypersecretion of growth hormone or of follicle-stimulating hormone and ACTH by the hypophysis has been suggested to be a cause of both diseases. (47 refs)

- 79-5486 Epithelial Injury by Cystoscopy Fluids.** (Eng) Weinstein, R. S. (Dept. Pathology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL 60612); Koo, C.; Pauli, B. U.; Jacobs, J. B.; Friedell, G. H. *Semin Oncol* 6(2): 257-259; 1979.

The possibility that cystoscopy fluids may enhance the spread of bladder cancer cells was suggested by observations in laboratory animals. Cancer cells introduced into mouse bladders in which the epithelium had been altered by chemical or thermal trauma were capable of implanting and growing. In addition, exposure of bladder mucosa of normal and tumor-bearing rats to cystoscopy infusion fluids caused epithelial necrosis. Epithelial proliferation occurred as a response to the injury. (4 refs)

- 79-5487 Unilateral Abdominal Cryptorchidism.** (Eng) Hinman, F. (M-553, Univ. California, San Francisco, CA 94143). *J Urol* 122(1): 71-75; 1979.

The unilateral nonpalpable undescended testis, one entity of the cryptorchidism complex, is more prone to malignancy. The risk of

malignancy is 35 times greater for persons with cryptorchidism than for the general population. Intraabdominal testes have an even higher risk of malignancy. Although no more than 15% of undescended testes are intraabdominal, they contain half of the tumors. Testicular dysgenesis rather than exposure to increased temperature appears to be the major factor leading to neoplasia, as the testis is subjected to the same elevated temperature whether it is within the abdominal cavity or lying in the groin. It has been asserted that early orchiopexy reduces the likelihood of malignancy, but no convincing evidence has been presented. The risk of eventual death from carcinoma in a prepubertal boy with an abdominal testis is almost 6%, much higher than the 0.2% chance of a fatal outcome from orchiectomy. The risk of malignancy is concluded to be great in an abdominal testis, whether up or down, and probably warrants its removal when there is a contralateral testis. (73 refs)

- 79-5488 Gastric Stump Carcinoma--Carcinogenic Factors and Possible Preventive Measures. (Eng) Schonleben, K. (Abt. Allgemeinchirurgie, Chirurgische Universitätsklinik, Jungeblutplatz 1, 4400 Munster, W. Germany); Langhans, P.; Schlake, W.; Kautz, G.; Bunte, H. *Acta Hepatogastroenterol (Stuttg)* 26(3): 239-247; 1979.

Clinical experience with gastric stump carcinoma is reviewed. The type of procedure used in the primary resection and the local irritation accompanying execution of the anastomosis may be involved in the etiology of the malignant transformation. The use of resorbable sutures and a surgical procedure that avoids reflux is recommended. Periodic postoperative radiologic, endoscopic, and histologic studies are essential. (46 refs)

- 79-5489 Ultrastructure of Hepatocellular Tumors. (Eng) Hruban, Z. (Dept. Pathology, Univ. Chicago, Chicago, IL). *J Toxicol Environ Health* 5(2/3): 403-431; 1979.

The lesions that appear during hepatocarcinogenesis in the rat can be separated into morphologically different entities which, when arranged in sequence, are thought to be the morphological stages in the carcinogenic process. The primary and transplantable hepatocellular carcinomas can also be arranged in a sequence thought to represent the progression toward the ultimate cancer cell. Studies of rat, murine and human hepatocarcinogenesis are reviewed. Hepatocellular tumors have been induced in the rat by nitrosomorpholine, diethylnitrosamine, N-2-fluorenylacetylamide, azo compounds and other carcinogens. Lesions derived from hepatocytes can be differentiated from those originating in other cellular components of the liver. In the early stages of carcinogenesis, there is variability and divergence in the structure of cellular organelles; the cellular structure and organelles become more simplified with progression of the cancer, and no qualitative changes specific for cancer cells exist. Toxic changes associated with the carcinogenic process are listed. As hepatocellular cancer progresses, decreases are observed in the number and complexity of microbodies, reductions are seen in the mitochondrial cristae and the tubulovesicular form of smooth reticulum, accumulation of free ribosomes occurs, increases are observed in the granular component, and condensation of the fibrillar component is seen. The neoplastic tissue exhibits an increased mitotic rate. (132 refs)

- 79-5490 Pathology of Primary Liver Cancer. (Eng) Lapis, K. (First Dept. Pathology, Semmelweis Medical Univ.,

Budapest, Hungary); Johannessen, J. V. *J Toxicol Environ Health* 5(2/3): 315-355; 1979.

Current knowledge of the etiology and pathogenesis of primary hepatocellular carcinoma (PHC) in humans is briefly reviewed; and the gross, histopathologic, and ultrastructural features of the variants of this tumor are emphasized. The geographic variations in PHC frequency are attributable in part to the occurrence of carcinogens such as aflatoxin B1, other aflatoxins, cycasin and pyrrolizidine alkaloids. The association of PHC and liver cirrhosis is discussed, as is the oncogenic effect of hepatitis B virus. The relationships between hormone treatment and the development of liver cell carcinoma and between continuous use of oral contraceptives and liver cell adenomas are mentioned. The pathology of PHC is discussed with regard to the gross appearance, light microscopic findings, and electron microscopic appearance. Difficulties in differential diagnosis occur mainly when the tumors are of the combined or mixed type, contain formations that resemble bile ducts, or when they are undifferentiated or of the clear cell variety. The mode of spread of PHC is reviewed. The prognosis of PHC is very poor due to the late diagnosis. (181 refs)

- 79-5491 Precancerous Changes in the Human Liver. (Eng) Anthony, P. P. (Dept. Pathology, Univ. Exeter, Exeter, Devon, England). *J Toxicol Environ Health* 5(2/3): 301-313; 1979.

There is comparatively little knowledge of the cellular events that precede neoplasia in the human liver. Cirrhosis is a common antecedent or accompaniment of liver cell carcinoma, and it seems that both its etiology and its duration are relevant risk factors. Many cellular changes have been observed in patients and among populations considered to be at risk. Of these, liver cell dysplasia is the most striking, and studies of its prevalence, natural history, and association with particular forms of cirrhosis suggest that it is a precancerous change. Bile duct carcinoma may follow infestation with liver flukes and ductal epithelial hyperplasia is present before the development of cancer. Angiosarcoma from several causes is commonly preceded by portal and capsular fibrosis, vascular changes, and Kupffer cell hyperplasia. (50 refs)

- 79-5492 Hepatocyte Suspensions and Cultures as Tools in Experimental Carcinogenesis. (Eng) Seglen, P. O. (Dept. Tissue Culture, Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Montebello, Oslo, Norway). *J Toxicol Environ Health* 5(2/3): 551-560; 1979.

Techniques for the isolation of preneoplastic cell populations and their application in the analysis of the development of liver cancer are discussed. The preparation and purification of isolated rat hepatocytes can be accomplished in the following steps: 1) a two-step collagenase perfusion of the isolated rat liver using Ca^{2+} free buffer in the first 10 min and collagenase with Ca^{2+} for 10 min; 2) mechanical disruption of the collagenase-perfused tissue with a stainless steel comb; 3) filtration through a nylon mesh; 4) purification of hepatocytes by differential centrifugation. Thus far, transformed cells have not been separated from normal hepatocytes in the cell suspensions obtained after collagenase dispersion of the liver. The application of hepatocyte cultures to the screening of chemical carcinogens is discussed as a possible supplement to the bacterial test systems currently in use. Although proliferating cultures of true hepatocytes have not been established, these cells would make an ideal system for the testing of cell

transformation by chemical carcinogens. Further work is needed. (75 refs)

- 79-5493 The Pattern of Disease in the Post-infection Era: National Trends. (Eng) Doll, R. (Dept. Regius Professor Medicine, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, England). *Proc R Soc Lond [Biol]* 205(1158): 47-61; 1979.

Trends in mortality among British infants, children, and persons aged 45-64 yr during 1931-1975 are reviewed. Among infants, all causes of death except congenital anomalies have decreased, and mortality among children aged 1-14 yr has decreased by nearly 90%. The remaining mortality among children is largely due to violence (32%), neoplasms (17%), and congenital anomalies (15%). Trends in mortality from the principal types of childhood cancer have shown downward trends for several types, including leukemia, Hodgkin's disease, and Wilms' tumor. Among individuals aged 45-64 yr, mortality since 1931 has decreased by 23% in men and by 42% in women. Lung cancer (34% of deaths in this age group) and ischemic heart disease (31%) are among several causes of death that have become more common in this age group, although the rates have declined since 1975. Mortality from cancer of the stomach declined significantly among both men ($p < 0.01$) and women ($p < 0.05$) between 1970 and 1975, whereas non-Hodgkin's lymphoma among men ($p < 0.05$) and cancers of unspecified site among women ($p < 0.05$) have become more common. In total, cancers of 25 sites have varied $<1\%/yr$ since 1931, cancers of 16 sites have decreased progressively by $>1\%/yr$, and cancers of 13 sites have increased by $>1\%/yr$. (9 refs)

- 79-5494 Endocrine Effects of Oral Contraception. (Eng) MacLeod, S. C. (70 Exhibition St., Kentville, Nova Scotia, Canada B4N 1K5). *Int J Gynaecol Obstet* 16(6): 518-524; 1979.

The benefits and risks of oral contraceptive use are discussed, particularly with regard to post-pill amenorrhea. Since 1972, the overall incidence of pituitary adenomas in patients with post-pill amenorrhea or with spontaneous secondary amenorrhea increased from 0% to 26%. However, there is presently no good evidence to suggest that pituitary tumors are more frequent when the amenorrhea is associated with oral contraceptive use. (37 refs)

- 79-5495 Smoking Patterns by Occupation, Industry, Sex and Race (2 Letters to the Editor). (Eng) Bader, M. (No affiliation given); Sterling, T. D. *Arch Environ Health* 34(3): 189; 1979.

Criticism is made of the observation in blacks that a lower smoking rate (vs that for whites) coupled with an increased lung cancer rate is important additional evidence that occupation, and not smoking, bears the major responsibility for lung cancer in humans. Alternative reasons for this difference might include: (a) black men smoke different brands of cigarettes than white men; (b) black men smoke a cigarette more completely than white men; (c) blacks have a 12%-14% smaller vital capacity than whites; and (d) there might be significant differences in age distributions of the black and white smoking populations. A rebuttal to this criticism is given. (6 refs)

- 79-5496 Cancer Mortality Among Low-Risk Populations. (Eng) Enstrom, J. E. (Cancer Epidemiology, UCLA Sch. Public Health, UCLA, Los Angeles, CA). *UCLA Cancer Cent Bull* 6(3): 3-7; 1979.

The cancer mortality experience among the major low-risk populations in the US is reviewed. Over an 8-yr period, the mortality rates for cancer sites related to cigarette smoking or alcohol consumption were extremely low among a group of 47,000 Seventh-Day Adventists living in California. In addition, the risk of death from cancers of the colon, stomach, and pancreas was about 60%-70% that of the general US population, and for women the risk of postmenopausal deaths from cancers of the breast, ovary, and uterus was significantly below that of the general population; dietary factors were suggested as possible reasons for these findings. Compared with US whites, the cancer mortality ratio among Mormons during 1968-1975 was 66% for men and 81% for women. The total cancer death rate among active Mormon men >35 yr old living in California is approx 50% that of US white men. The remaining life expectancy for these Mormons is 44.6 yr, 8 yr longer than that of US white men in 1970. The cancer death rates among Mormons were lower than those expected for all sites except the prostate and except for lymphomas and leukemias. Cancer mortality rates among US nonsmokers were 58%-76% lower than those for US whites. The most plausible explanation is that the lack of smoking per se reduces the total cancer rate by a substantial amount. Other factors that appear likely to have the greatest impact on cancer mortality are personal health habits, diet, socioeconomic status, and certain host factors related to aging. (10 refs)

- 79-5497 Socioeconomic Aspects of Lung Cancer. (Fre) Saracci, R. (Unite d'epidemiologie et de biostatistique, Centre international de recherche sur le cancer, 150 cours Albert Thomas, F-69372 Lyon Cedex, France). *Schweiz Med Wochenschr* 109(22): 820-824; 1979.

The lung cancer incidence and mortality rates in Switzerland are reviewed and compared with those in other industrialized nations. From 1970 to 1972, the annual incidence of lung cancer (per 10^5 subjects) in Geneva was 60.4 in men and 7.5 in women; the respective rates in Connecticut, Birmingham (England), and Hamburg were 77.1 and 11.5, 53.7 and 12.2, and 63.0 and 9.2. In 1972, the annual lung cancer mortality rate in Switzerland was 42.6/ 10^5 men and 4.1/ 10^5 women, similar to the rates in West Germany, the US, and Italy. (22 refs)

- 79-5498 The Case-Referent (Case-Control) Study in Occupational Health Epidemiology. (Eng) Axelson, O. (Dept. Occupational Medicine, Univ. Hosp., Linköping, Sweden). *Scand J Work Environ Health* 5(2): 91-99; 1979.

The case-referent type of study requires less extensive data acquisition than the cohort approach and can be used to determine relative risk and absolute mortality and morbidity rates. It is also possible with this method to study the etiologic influence of several exposures within the same series of cases and referents. However, there are many methodological pitfalls which can form a source of bias in a case-referent study. These include those relating to the role of exposure status in the selection of cases and/or referents, inaccuracy of the information on exposure among cases and referents, the possible relation of reference entity (usually various noncase diagnoses) to the exposure, and incomplete control of

confounding factors. Due to the close relationship between case-referent studies and proportional mortality studies, there is rarely a need for the proportional mortality approach. A study of arsenic as a possible cause of lung cancer and other types of malignancies and cardiovascular disease is given as an example of the case-referent method. (21 refs)

- 79-5499 Effect of Lead on Reproduction. (Hun) Peter, S. (Humangenetikai Laboratorium, Országos Kozegszegügyi Intezet, Budapest, Hungary); Czeizel, E. *Egeszsegudomány* 23(2): 180-187; 1979.

Studies of the effects of lead on reproduction are reviewed. Lead was found to have teratogenic effects in rats and golden hamsters and mutagenic effects in some experimental animals. No chromosome aberrations were seen in occupationally exposed subjects. (81 refs)

- 79-5500 Are Malignancies Increased in Uremia? (Eng) Kjellstrand, C. M. (Univ. Minnesota Hosps., Minneapolis, MN 55455). *Nephron* 23(4): 159-161; 1979.

Literature suggesting a possible relationship between uremia and malignancy is reviewed, and the types of neoplasms and the diagnoses of renal failure in 35 patients are listed. The most common cancer sites were the kidney (6 patients) and skin (5 patients). The most common types of renal failure were polycystic kidney disease (8 patients) and chronic pyelonephritis (6 patients). It seems probable that the incidence of malignancies is increased by chronic uremia and chronic hemodialysis. (24 refs)

- 79-5501 Pancreatic Cancer. An Overview of Epidemiology, Clinical Presentation, and Diagnosis. (Eng) Malagelada, J. R. (Gastroenterology Unit, Div. Gastroenterology and Internal Medicine, Mayo Clinic, Rochester, MN 55901). *Mayo Clin Proc* 54(7): 459-467; 1979.

The epidemiology, clinical presentation, and diagnosis of pancreatic cancer are reviewed. Pancreatic cancer is a common and lethal neoplasm whose etiological factors have not been identified. Pancreatic cancer is rarely diagnosed early. The most common prediagnosis symptoms are wt loss, abdominal pain, and jaundice, all of which may be symptoms of other malignant and nonmalignant diseases. Results of routine laboratory tests are often within normal limits, even in the presence of metastatic disease. Among the more invasive tests and imaging techniques that are being used are pancreatic function tests and pancreatic juice cytology, various techniques for visualizing the pancreas, and nonoperative biopsy techniques. A study of 70 patients suspected of having pancreatic cancer in whom routine diagnostic tests were negative showed that the endoscopic retrograde pancreatogram and arteriogram were the most sensitive and specific tests for detecting pancreatic cancer and differentiating between cancer and pancreatitis. Abdominal ultrasonography should be performed first when pancreatic cancer is suspected. If results are negative, pancreatic exocrine function tests should be done, and positive results from either procedure should be followed up with endoscopic retrograde pancreatography. (67 refs)

- 79-5502 Hepatic Cancers in Man: Quantitative Perspectives. (Eng) Popper, H. (Stratton Lab. Study Liver Diseases, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029). *Environ Res* 19(2): 482-494; 1979.

The worldwide distribution and incidence of malignant hepatic tumors (hepatocellular carcinoma, hepatoblastoma, intrahepatic bile duct carcinoma, and hepatic angiosarcoma) are reviewed, along with the etiologic factors involved. The geographic distribution of human hepatic malignancies strongly suggests a causative role of environmental factors. The vast majority of these malignancies in all areas of the world is usually associated with cirrhosis and one of three factors: hepatitis B infection, alcoholism, or aflatoxin exposure. The greatest chance for prevention lies in limiting hepatitis B infection. Although they constitute only a very small number of all hepatic malignancies, some tumors not associated with cirrhosis have been caused by industrial and therapeutic factors. A large number of environmental or industrial agents are carcinogenic in animals, but there is no conclusive evidence of their hepatocarcinogenicity in humans. Nevertheless, these substances may alter the hepatic metabolism with consequences for the liver and other organs. (93 refs)

- 79-5503 Role of Oral Contraceptive Agents in the Pathogenesis of Liver Tumors. (Eng) Nissen, E. D. (Univ. California, Coll. Medicine, Irvine, CA); Kent, D. R.; Nissen, S. E. *J Toxicol Environ Health* 5(2/3): 231-254; 1979.

Data from the Registry for Liver Tumors Associated with Oral Contraceptives on 90 women with liver tumors who had taken oral contraceptives are reviewed. More than 75% of the patients were <35 yr old. Most patients were exposed to mestranol (ME) alone or alternately with ethinylestradiol, both synthetic steroidal estrogens. Inability to demethylate ME in the smooth endoplasmic reticulum of hepatocytes may allow massive accumulation of oncogenic metabolites. This is probably a pharmacogenetic variable in a small number of women. Cholestasis, hypervascularity, induction of intracellular enzyme systems, thrombogenesis, and thickening of arterial and venous walls are other known effects of synthetic estrogens and progestogens. All may contribute to the pathogenesis of liver tumors. Many patients are asymptomatic until there is rapid expansion of the tumor. Pain occurs when Glisson's capsule stretches. Intrahepatic bleeding and liver rupture are common sequelae. Ligation of the hepatic artery may be lifesaving in the face of exsanguinating liver bleeding. Reports of regression with observation alone are encouraging. Instances of progression of unresected adenomas to rupture during subsequent pregnancy dictate avoidance of sex steroids in patients with hepatic neoplasia. Sonography, computerized axial tomography, radionuclide scans, and selective celiohepatic angiography are useful methods for the diagnosis of liver tumor in the symptomatic patient. There is a primary need to develop biochemical methods for detecting patients at risk for developing liver tumors. Epidemiologic research and central reporting of case histories are needed in the search for common factors. (17 refs)

- 79-5504 Proceedings of the Symposium: Early Gastric Cancer. (Eng) Kawai, K. (Dept. Preventive Medicine, Kyoto Prefectural Univ. Medicine, Kyoto, Japan); Misaki, F.; Kohli, Y.; Ida, K.; Ramirez Ramos, A. *Gastroenterol Jpn* 14(3): 266-271; 1979.

The occurrence and growth characteristics of gastric cancer in

humans are reviewed. Because the experimental gastric cancers induced in dogs with N-methyl- or N-ethyl-N'-nitro-N-nitrosoguanidine are dissimilar from those seen in humans, knowledge gained from animal experiments cannot be applied directly to human subjects. The incidence of gastric cancer is very high among the Japanese, and atrophic gastritis, which is almost always associated with intestinal metaplasia of the gastric mucosa, appears in younger age groups among the Japanese than among other populations. It appears that well-differentiated gastric carcinoma has a much closer relation to intestinal metaplasia than does undifferentiated cancer. The rate of malignant change in gastric ulcers appears to be very low. The doubling time of early gastric cancer varies with histologic type and depth of invasion, ranging from 2 to 10 yr in the depressed types that are most commonly encountered. Early gastric cancers with small diameters apparently grow slowly, whereas those with large diameters grow more rapidly. The change from early to advanced cancer involves a change from Borrmann type IIb to types IIc or IIc + III; some cases may go directly to Borrmann type IV. (6 refs)

- 79-5505 Cholesterol and Colon Cancer (Letter to Editor). (Eng) Cruse, P. (Surgical Unit, Rayne Inst., Univ. Coll. Hosp. and Medical Sch., London WC1E 6JJ, England); Lewin, M.; Clark, C. G. *Lancet* 2(8132): 43-44; 1979.

Information indicating that lack of dietary fiber plays no primary role in human colon carcinogenesis is reviewed, and nine publications that fail to substantiate the association of either colonic bacteria or increased fecal bile acids with colorectal cancer risk are cited. Evidence indicating that increased fecal cholesterol excretion and decreased fecal cholesterol degradation are related to colorectal cancer risk is presented. (26 refs)

- 79-5506 Food and Nutrition in the Netherlands; Fighting the Consequences of Prosperity. (Dut) Hautvast, J. G. (Vakgroep Humane Voeding, Landbouwhogeschool, Wageningen, Netherlands); Hermus, R. J. *Ned Tijdschr Geneesk* 123(22): 939-944; 1979.

The influence of current dietary habits on the incidence of cardiovascular diseases and cancer in the Netherlands is discussed. Current hypotheses (related to intractable constipation and small feces volume, high meat consumption, alterations of gallbladder metabolism) to explain the observed correlation between nutrition pattern and the incidence of colon cancer are briefly presented. (no refs)

- 79-5507 Epithelial Proliferative Disease of the Breast - A Marker of Increased Cancer Risk in Certain Age Groups. (Eng) Rogers, L. W. (Dept. Pathology, Carraway Methodist Hosp., Birmingham, AL); Page, D. L. *Breast* 5(2): 2-7; 1979.

The results of a 20-yr follow-up study of 925 women who had benign breast biopsies, and a survey of the literature suggest that certain histologic patterns of epithelial proliferative breast disease indicate an increased risk for subsequent mammary carcinoma. This risk in the follow-up study was four to six times that of the general population if atypical lobular hyperplasia was present and

two to three times if ductal hyperplasia was present in a patient >45 yr old. There was no increased risk if the patient was younger than 45 yr or if sclerosing adenosis was present. (13 refs)

- 79-5508 Pregnancy and Lactation in Relation to Breast Cancer Risk. (Eng) Vorherr, H. (Dept. Obstetrics-Gynecology and Pharmacology, Univ. New Mexico, Sch. Medicine, 915 Stanford Drive N.E., Albuquerque, NM 87131). *Semin Perinatol* 3(3): 299-311; 1979.

The effects of pregnancy and lactation on the risk of breast cancer (BC) are reviewed. Pregnancy early in life appears to protect against BC, with the prolonged periods of mitotic rest of the breast tissue during gestation and lactation and the increase in certain hormones (estriol and progesterone) having been suggested as potential mechanisms of protection. However, it is unlikely that estriol protects against BC. BC risk appears to be fourfold greater in women whose first pregnancy occurs after 30-35 yr of age than in nulliparous women of the same age group. However, the assumption of a protective effect of early pregnancy and the deleterious effect of late pregnancy is not uniformly agreed upon. The clearance of mammary carcinogens via the milk, mitotic rest, and nutritional and immunologic factors have been suggested as potential mechanisms of the protective effect of nursing. Some investigators believe that lactation has little or no effect on BC risk. In a certain strain of mice, a mammary RNA-type tumor virus is transmitted through the milk and causes adenocarcinoma in almost all offspring. About 10%-20% of lactating women have viruslike particles with RNA-dependent DNA polymerase activity in their milk. A specific relationship between mouse mammary tumor virus and these particles has been suggested, although some researchers suggest that the "virus" particles in human milk are only artifacts. The possible role of prolactin in the development and maintenance of human BC is questioned. (118 refs)

- 79-5509 Teenagers and Contraception. (Eng) Rozenbaum, H. (15 Rue Daru, 75008 Paris, France). *Int J Gynaecol Obstet* 16(6): 564-567; 1979.

Among the factors physicians should take into account when prescribing contraceptives for teenagers are cytologic abnormalities in young women. One study showed that the incidence of cervical dysplasia (20%) in girls under 19 yr of age has increased five times since 1971. In two other studies, the incidences of cytologic abnormalities in young women were 1.7% and 4.8%, respectively. The risk of cervical cancer seems to be associated with low socioeconomic level, sexual intercourse at an early age and a diversity of partners, and herpes simplex virus type 2 infection. (13 refs)

- 79-5510 Discussion Summary on Measurement of Carcinogenic Risk. (Eng) Davis, W. (Res. Training and Liaison Unit, International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Rosenfeld, C. *IARC Sci Publ* (25): 229-233; 1979.

A discussion of the measurement of carcinogenic risk is summariz-

ed. In order to compare carcinogens, common units have to be agreed upon. However, there is no obvious correlation between a dose of radiation and the dose generated in vivo from a chemical carcinogen in which reactive electrophiles must be generated in situ from the small proportion of the dose that reaches the target organ or tissue. In addition, mixed or sequential exposures occur. Insufficient work has been done on summation of risks. In doing so, substances should be considered in one of two categories: (1) those acting through direct interference with the genetic system (for which a no-toxic-effect level cannot be accepted) and (2) those acting in other ways (for which no-toxic-effect levels ought to be set). Although there are several mathematical models for calculating risk based on the extrapolation from high doses given to animals to the much lower doses that constitute human exposure, none have been accepted, and the validity of such extrapolations is uncertain. Experiments should be large enough to establish upper confidence limits on the dose required to induce cancer or to give wt to a negative result. Confidence limits should be included in all experimental and epidemiological reports. A variety of animal species and strains must be studied to determine which most resemble humans in susceptibility to a wide range of carcinogens. An important distinction between animal experiments and human observations is time: the former are generally predictive, whereas the latter are generally retrospective. Negative epidemiological findings in humans are important, because human observations take into account such factors as biological availability of the potential carcinogen in the environment. Among the many difficulties in the interpretation of epidemiological data, however, are the quantification of exposures and the computation of expected numbers. It is unclear what wt should be given to studies in which only benign tumors are found. More attention must be paid to en-

vironmental pollutants and their interactions in evaluating cancer risk. (no refs)

- 79-5511 Biochemical Regulators of Bone Resorption and Their Significance in Cancer. (Eng) Martin, T. J. (Dept. Medicine, Univ. Melbourne, Victoria 3081, Australia); Atkins, D. *Essays Med Biochem* 4: 49-82; 1979.

The biochemical regulators of bone resorption are reviewed, along with their significance in cancer. Cancer patients can be classified into four main groups: those with hypercalcemia (HC) in association with a nonparathyroid neoplasm that has not metastasized to bone (Group I); those with HC in association with metastatic cancer growth in bone (Group II); those with metastatic cancer in bone but without HC (Group III); and those with HC in association with multiple myeloma, lymphoma, or leukemia (Group IV). The major known humoral influences on bone resorption are parathyrin, prostaglandins, osteoclast-activating factor, vitamin D, osteolytic sterols, and calcitonin. There are valid arguments against the hypothesis that Group I cancers are related to parathyrin, and it appears that most such patients have HC caused by some other humoral factor. HC in some animal syndromes appears to be due to the production of a prostaglandin by tumor cells, and prostaglandins may have a role in the establishment of bony metastases and in the promotion of osteoclastic resorption around the sites of established metastases. Osteoclast-activating factor or some related agent appears more likely to be involved in Group IV cases than prostaglandins. The relationships, if any, of vitamin D, osteolytic sterols, and calcitonin to HC in malignancy have not been demonstrated. (123 refs)

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CHEMICAL CARCINOGENESIS

- 79-5512 Chromosome Studies in Patients Treated with Chemotherapy for Trophoblastic Tumours. (Eng) Lawler, S. D. (Dept. Cytogenetics and Immunology, Royal Marsden Hosp., Fulham Rd., London, SW3 6JJ, England); Walden, P. A. In: *Mutagen-Induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 239-246; 1978.

Lymphocyte and bone marrow chromosomes of patients treated by chemotherapy for trophoblastic tumors were monitored for the frequency of aberrations before, during, or after treatment. The patients were selected from three groups: low risk, medium risk and high risk. The patients in the low-risk group showed no evidence of a damaging effect of therapy (methotrexate + folinic acid) on the chromosomes of the lymphocytes. Those in the medium-risk group showed increased chromosome damage following therapy, (methotrexate + seven other drugs), but the increase was not judged sufficient to cause concern. Patients on intensive therapy (seven or eight drugs + radiotherapy) showed a very high frequency of chromosome damage in their lymphocytes. Damage to bone marrow chromosomes was unremarkable in all groups. In general, survivors showed little evidence of genetic damage to somatic cells. (11 refs)

- 79-5513 Cytogenetic Effects of Chemotherapy and Cranial Irradiation on the Peripheral Blood Lymphocytes of Children with Leukaemia. (Eng) Fischer, P. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A 1090 Vienna, Austria); Nacheva, E.; Pohl-Ruling, J.; Krepler, P. In: *Mutagen-Induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 247-257; 1978.

Children with leukemia were compared with children treated for nonmalignant disease in order to determine if there is an increased tendency to breakage in the normal chromosomes of leukemic children and whether treatment, particularly cranial irradiation, produces chromosome aberrations. The leukemia group (34 children aged 3-11 yr) included 32 children with acute lymphocytic leukemia (ALL), 30 of whom had received cranial irradiation (2,400 rads) in addition to intensive chemotherapy; the 2 other children, one with acute myeloid leukemia (AML) and one with chronic myeloid leukemia (CML), had had chemotherapy only. The nonmalignant (NM) group consisted of 18 children, aged 2-14 yr, all with nephrosis; 9 were on cortisone treatment alone and 9 cortisone-resistant patients were treated with additional chemotherapy. The chromatid aberration rate of the leukemia group prior to treatment did not differ significantly from that of the NM group (4.1% gaps, 0.8% breaks). Cells from the ALL group and the AML and CML patients, analyzed 1.2, 8.3, and 46 mo after the start of chemotherapy, showed steady increase in gaps (mean values of 5.9, 7.3, and 12.0%), but rates of breaks in chromatids fluctuated (3.4% at 1.2 mo, 1% at 8.3 mo, 5.3% at 46 mo). Two-break aberrations (dicentrics and minutes) appeared only after 36 mo of chemotherapy. The cells from ALL patients treated with cranial irradiation showed decreased chromatid aberration rates immediately after irradiation (4.4% gaps and 1.4% breaks as against 5.9% gaps and 3.4% breaks in patients prior to

radiation). Chromosome aberrations of both types were present at all periods. The following conclusions were reached: (1) prolonged, intensive chemotherapy causes a significant rise in chromatid aberrations, both gaps and breaks; (2) after 2 yr of treatment, chemotherapy alone causes a small, significant increase in chromosome breaks; (3) radiation of 2,400 rads to the cranial area and medulla oblongata causes an immediate, sharp rise in chromosome aberrations and concurrent drop in chromatid aberrations. No evidence of an increased, spontaneous breakage rate in the normal chromosomes of leukemic children was found. (26 refs)

- 79-5514 Toxic and Mutagenic Effects of Carcinogens on the Mitochondria of *Saccharomyces cerevisiae*. (Eng) Egilsson, V. (Dept. Botany and Microbiology, Univ. Coll. London, Gower St., London WC1E 6BT, England); Evans, I. H.; Wilkie, D. *Mol Gen Genet* 174(1): 39-46; 1979.

Nineteen haploid yeast (*Saccharomyces cerevisiae*) strains were used to assess the relative growth inhibitory potencies on fermentable vs nonfermentable media of a series of carcinogenic and noncarcinogenic chemicals. The majority of the carcinogens were distinctly more potent on the nonfermentable (glycerol) medium, where mitochondrial function was required for growth, than on the fermentable medium, where it was not. The antimitochondrial selectivity indicated by these growth tests was much less for the noncarcinogens. Similarly, most carcinogens induced the cytoplasmic petite mutation, whereas the noncarcinogens did not. Five carcinogens impaired the development of cytochromes *aa₃* and *b* in glucose cultures. Six carcinogens inhibited growth on three fermentable sugars, the utilization of which requires mitochondrial function. Of five carcinogens examined, four suppressed the surface-dependent phenomenon of flocculence in a flocculating strain of yeast at concentrations primarily affecting the mitochondrial system. The fifth carcinogen had a similar but less pronounced effect. (45 refs)

- 79-5515 Synthesis of the Glucuronic Acid Conjugate of Methylazoxymethanol. (Eng) Matsumoto, H. (Dept. Agricultural Biochemistry, Univ. Hawaii, 1800 East-West Road, Honolulu, HI 96822); Takata, R. H.; Komeiji, D. Y. *Cancer Res* 39(8): 3070-3073; 1979.

The synthesis of methylazoxymethyl- β -D-glucopyranosiduronic acid (MAM-GlcUA), its physical and biochemical properties, and its acute toxicity and mutagenicity are described. MAM-GlcUA was synthesized by oxidizing the primary alcohol of the glucose moiety of cycasin (methylazoxymethanol- β -D-glycopyranoside) to a carboxylic acid. The oxidation was carried out by bubbling oxygen gas through a cycasin soln in the presence of a platinum-on-carbon catalyst. A band at $1,715\text{ cm}^{-1}$, not present in the cycasin infrared spectrum, appeared in the spectrum of the oxidized cycasin product, establishing the presence of a carboxylic acid group. The oxidation product was MAM-GlcUA, because when it was hydrolyzed with *Escherichia coli* β -glucuronidase, it produced methylazoxymethanol and glucuronic acid. In addition, the β -glycosidic linkage of cycasin was retained. When varying quan-

ties of the synthesized MAM-GlcUA were injected into Wistar rats of both sexes and of varying wts, they were not acutely toxic. The compound was mutagenic to *Salmonella typhimurium* when preincubated with *E. coli* β -glucuronidase, but not when it was preincubated with bovine liver glucuronidase. (19 refs)

- 79-5516 Inhibitory Effects of Butylated Hydroxyanisole on Methylazoxymethanol Acetate-induced Neoplasia of the Large Intestine and on Nicotinamide Adenine Dinucleotide-dependent Alcohol Dehydrogenase Activity in Mice. (Eng) Wattenberg, L. W. (Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN 55455); Sporn, V. L. *J Natl Cancer Inst* 63(1): 219-222; 1979.

A study was carried out to determine whether butylated hydroxyanisole (BHA), an antioxidant food additive, could inhibit methylazoxymethanol acetate (MAM acetate)-induced large-bowel carcinogenesis in female CF₁ mice. Mice of 8 or 11 wk of age received diets containing 5 or 10 mg BHA/g diet and sc injections of MAM acetate (0.3 mg 2x/wk for 3 wk or 0.2 mg 2x/wk for 3 wk followed by 0.3 mg 2x/wk for 3 wk). BHA was added to the diet 9 days before the first injection of MAM acetate and withdrawn 1 day after the final injection. Mice were sacrificed and autopsied at 46 or 51 wk of age. Approx 40% of 72 control mice given only MAM acetate developed large intestinal adenomas and/or adenocarcinomas, whereas only 5% of 39 mice receiving the 5-mg/g BHA diet and none of 17 mice receiving the 10-mg/g BHA diet developed these neoplasms. The inhibitory effects of BHA [0.01-2.0 micromoles (μ mol)/ml reaction mixture] on the activity of unpurified liver and large intestine NAD⁺-dependent alcohol dehydrogenase (a postulated activating enzyme for MAM acetate), using a substrate concentration of 16 μ mol/ml reaction mixture, were not concentration-dependent: 0.5 μ mol BHA reduced the activity to 34%-56% of control levels, but higher BHA concentrations resulted in little additional inhibition. These results suggest that more than one protein catalyzes the alcohol dehydrogenase reaction. The parallel finding of BHA inhibition of MAM acetate carcinogenesis of the large bowel and of NAD⁺-dependent dehydrogenase activity supports the postulated role of the dehydrogenase activity in activating MAM to an ultimate carcinogenic form. However, BHA has multiple biologic actions, so that its inhibitory effect on MAM acetate-induced neoplasia of the large intestine may entail some other mechanism. (14 refs)

- 79-5517 Mechanism of Inhibition of Hepatic Protein Synthesis in Rats by the Carcinogen, Methylazoxymethanol Acetate. (Eng) Grab, D. J. (Dept. Cell Biology, Rockefeller Univ., 1230 York Ave., New York, NY 10021); Pavlovic, A.; Hamilton, M. G.; Zedeck, M. S. *Biochim Biophys Acta* 563(1): 240-252; 1979.

Weanling male Sprague-Dawley rats were used to determine which of the components necessary for hepatic protein synthesis are affected by the potent carcinogen methylazoxymethanol acetate (MAMA). Incubation of microsomes and the high speed supernatant fraction from livers of rats treated 1 hr previously with MAMA (35 or 70 mg/kg) resulted in an approx 67% and 77% inhibition, respectively, of L-(4,5-³H)leucine incorporation into protein. Fractions from the livers of rats treated with dimethylnitrosamine (DMN, 30mg/kg) were inhibited by 50%. Both MAMA and DMN appeared to act at the level of the polysome. Free polysomes were isolated from the livers of rats 1 hr after treatment with 70 mg/kg MAMA. After 30 min incubation,

when protein synthesis had ceased to be linear, the free, membrane-derived and membrane-bound polysomes were each inhibited by approx 40%-50%. MAMA disaggregated the polysomes to lighter polysome species. Poly(U)-directed polyphenylalanine synthesis by native ribosomal subunits was greater in preparations isolated from rats treated with carcinogen than in saline-treated controls. Moreover, the native ribosomal subunit fraction from treated livers was able to synthesize a protein similar in mol wt to globin in response to added rabbit globin messenger RNA (mRNA). These studies show that MAMA does not induce significant alterations in ribosomal subunits or initiation factors and suggest that the inhibition of protein synthesis and disaggregation of polysomes may result from an alteration in cytoplasmic mRNA or from the association of this mRNA with ribosomes. (45 refs)

- 79-5518 Environmental Factors Affecting Monooxygenase Activity of Microsomal Fractions of Human Liver Biopsies (Meeting Abstract). (Eng) Boobis, A. R. (Dept. Clinical Pharmacology, Royal Postgraduate Medical Sch., Hammersmith Hosp., London W12 0HS, England); Brodie, M. J.; Bulpitt, C. J.; Davies, D. S. *Br J Pharmacol* 66(3): 426P-427P; 1979 (1 ref)

- 79-5519 Role of Pesticides in Hepatocarcinogenesis. (Eng) Sugar, J. (Res. Inst. Oncopathology, Budapest, Hungary); Toth, K.; Csuka, O.; Gati, E.; Somfai-Relle, S. *J Toxicol Environ Health* 5(2/3): 183-191; 1979.

The carcinogenicity of the herbicide 2,4,5-trichlorophenoxyethanol (TCPE), which is contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was tested in Swiss mice. Doses of 0.7-70.0 mg/kg TCPE containing 0.0007-0.007 μ g/kg TCDD were administered by gastric intubation once a week over a period of 1 yr. The incidence of liver tumors was doubled only in males given the two highest doses of TCPE (67.0 and 70 mg/kg: the tumor incidence was 48% and 58%, respectively, compared with 26% in controls. Reduction of the TCPE and TCDD doses to 1/10 and 1/100 of the max tolerated dose resulted in a reduced incidence of liver tumors to levels similar to that of controls. When two groups of mice were given the same dose of TCPE but hundredfold different doses of TCDD, no significant differences in the incidence of liver tumors resulted, indicating that TCDD in this dose range (0.0007-0.07 μ g/kg) did not influence tumor frequency and that TCPE was responsible for the tumor-enhancing effect. There was no predominance of any histological type of hepatocellular tumor, and cirrhosis never preceded tumor development. When the in vivo data were compared with data on the induction of microsomal aryl hydrocarbon hydroxylase and biphenyl 2-hydroxylase activities by TCPE and TCDD, there was no correlation between the carcinogenicity of the drugs and their ability to induce these two enzymes. (26 refs)

- 79-5520 Research Related to the Herbicide Buvinol, Especially for Possible Carcinogenicity. (Eng) Sugar, J. (Res. Inst. Oncopathology, Budapest, Hungary); Toth, K.; Somfai-Relle, S.; Bence, J. *IARC Sci Publ* (25): 167-172; 1979.

The toxicity and carcinogenicity of the new herbicide Buvinol, which contains 2,4,5-trichlorophenoxyethanol (TCPE), were evaluated in male and female Swiss mice. In long-term carcinogenicity tests, the po administration of the max tolerated dose (70 mg/kg) of TCPE, contaminated with 0.1 ppm 2,3,7,8-

tetrachlorodibenzo- p-dioxin (dioxin), increased the incidence of liver tumors in male mice; lower doses of TCPE (7.0 and 0.7 mg/kg) and dioxin did not influence tumor frequency. The tumors induced by 70 mg/kg TCPE + 0.1 ppm dioxin included 71 hepatomas, 34 hepatocellular carcinomas, and 5 cholangiohepatocellular carcinomas. Exposure of workers to TCPE during its production or use should be controlled and reduced. (8 refs)

- 79-5521 The Effect of Ethylene Dibromide on Differentiation of the Acrosome, Nucleus, and Transient Nuclear Appendages in Ram Spermatids. (Eng) Hrudka, F. (Dept. Veterinary Anatomy, Western Coll. Veterinary Medicine, Univ. Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0); ElJack, A. H. *J Ultrastruct Res* 67(2): 135-151; 1979.

The testes of Colombia rams treated with ethylene dibromide (EDB: 13.5 mg/kg/day sc, for 12 days) and castrated 22, 27, 32, or 38 days after treatment were studied histologically and electron microscopically. The EDB treatment disturbed the differentiation of the acrosome, nucleus, and transient nuclear appendages. The prime target was the acrosome, which was hit first and most during its growing phase, ie, the cap phase of spermiogenesis. The results were aplasia, hypoplasia, or hyperplasia; deformation of the acrosomic cap; vesicular inclusions of the acrosomic matrix; and lesions in the acrosome attachment to the nucleus. Some of these anomalies could be related to the aberrant morphology and activity of the Golgi complex. The drug also affected nuclear metamorphosis taking place in the third phase of spermiogenesis. The effect was expressed in abnormal chromatin condensation, disturbed sap elimination, and deviation from modal shaping. It is postulated that the nuclear metamorphosis is supported by a machinery consisting of the acrosome, caudal manchette, and Sertoli cell mantle. The acrosome assumes the key position, since it seems to be the prerequisite for cell polarization and the polarization essential for differentiation of the caudal manchette and Sertoli cell mantle. The absence of the acrosome accounted for the complete failure of nuclear shaping, but the lack of the other appendages accounted for a partial deviation from the modal nuclear shape. (25 refs)

- 79-5522 Pattern and Dynamics of Teratospermia Induced in Rams by Parenteral Treatment with Ethylene Dibromide. (Eng) ElJack, A. H. (Dept. Veterinary Anatomy, Coll. Veterinary Medicine, Ohio State Univ., Columbus, OH 43210); Hrudka, F. *J Ultrastruct Res* 67(2): 124-134; 1979.

The pattern and dynamics of the transient teratospermia induced in Colombia rams with ethylene dibromide (EDB: 7.8-13.5 mg/kg/day sc, for 12 days) were studied. Cytological, cytochemical, and electron microscopic investigations were made of ejaculated sperm before, during, and after treatment until full recovery. The teratospermia had a relatively constant pattern and was dose-dependent, although individual animals varied in susceptibility. It was preceded by a latent period of about 4 wk, reached its max between 9 and 12 wk, and dissipated between 14 and 16 wk after the start of treatment. EDB strongly inhibited motility and reduced the activity of nitroblue tetrazolium reductase, but there were no corresponding changes in tail morphology. Structural aberrations were found in order of decreasing frequency in the acrosome, nucleus, and mitochondrial sheath. (27 refs)

- 79-5523 Effects of Methylene Chloride, Trichloroethane, Trichloroethylene, Tetrachloroethylene and Toluene

on the Development of Chick Embryos. (Eng) Elovaara, E. (Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkau 1, SF-00290 Helsinki 29, Finland); Hemminki, K.; Vainio, H. *Toxicology* 12(2): 111-119; 1979.

The approximate LD₅₀ for trichloroethylene and trichloroethanes when determined 14 days after injection into the air space of fertilized chicken eggs (at 2, 3, and 6 days incubation) varied between 50 and 100 µmol/egg, and LD₅₀ for toluene, tetrachloroethylene, and methylene chloride were over 100 µmol/egg. These chemicals induced macroscopic malformations at doses of 5-100 µmol/egg. The teratogenic potential of the tested compounds decreased in the following order: 1,1,1-trichloroethane > trichloroethylene > methylene chloride, tetrachloroethylene, 1,1,2-trichloroethane > toluene. (23 refs)

- 79-5524 Mutagenicity Studies with Halothane in *Drosophila Melanogaster*. (Eng) Kramers, P. G. (Natl. Inst. Public Health, P.O. Box 1, Bilthoven, Netherlands); Burm, A. G. *Anesthesiology* 50(6): 510-513; 1979.

The ability of halothane (HT) to induce sex-linked recessive lethal mutations in *Drosophila melanogaster* was investigated. Adult male flies were exposed to 1,000 or 1,600 ppm (volume/volume) HT for 14 days or to 2,100 or 20,000 ppm HT for 1 or 2 days. In several experiments, mutation frequency was increased slightly. Pooled data from the 14-day experiments indicated that the increase was twice the spontaneous rate, just reaching 5% significance level. This was considered a borderline result, indicating, with a fair degree of probability, that HT has weak mutagenic activity under the conditions studied. (23 refs)

- 79-5525 Carcinogenicity of Halothane in Swiss/ICR Mice. (Eng) Baden, J. M. (Anesthesiology Service-112A, VA Hosp., 3801 Miranda Ave., Palo Alto, CA 94304); Mazze, R. I.; Wharton, R. S.; Rice, S. A.; Kosek, J. C. *Anesthesiology* 51(1): 20-26; 1979.

A simplified in vivo bioassay system was used to test the carcinogenicity of halothane (HT) in Swiss/ICR mice. HT was tested only at its max tolerated dose, and histologic examination was performed only on tumor masses and other grossly abnormal tissues found at necropsy. Two groups of 15 timed pregnant mice were exposed to 500 ppm (0.05%) HT or to compressed air for 2 hr on days 10-19 of pregnancy. Five days after birth, the offspring were similarly exposed three times weekly for 78 wk. After a 10-wk no-treatment observation period, all remaining mice were examined by necropsy. Mice dying or killed *in extremis* before final sacrifice at 88 wk of age also underwent complete gross necropsy, unless extensive cannibalism or autolysis precluded examination. The incidences of malignant tumors, hepatomas/hepatic nodular hyperplasias, and benign tumors in HT-treated mice were 7%, 6%, and 20%, respectively; there were similar incidences of these lesions in control animals. It is concluded that, under the conditions of this experiment, lifetime administration of HT at its max tolerated dose is not associated with an increased incidence of neoplasia in Swiss/ICR mice. (14 refs)

- 79-5526 Metabolic and Mutagenicity Studies on DDT and 15 Derivatives. Detection of 1,1-Bis(p-chlorophenyl)-

2,2-dichloroethane and 1,1-Bis(*p*-chlorophenyl)-2, 2, 2-trichloroethyl Acetate (Kelthane Acetate) as Mutagens in *Salmonella Typhimurium* and of 1,1-Bis(*p*-chlorophenyl) Ethylene Oxide, a Likely Metabolite, as an Alkylating Agent. (Eng) Planche, G. (Unit Chemical Carcinogenesis, Internatl. Agency Res. Cancer, 150 cours Albert-Thomas, 69372 Lyon, France); Croisy, A.; Malaveille, C.; Tomatis, L.; Bartsch, H. *Chem Biol Interact* 25(2/3): 157-175; 1979.

Using a novel in vitro technique whereby microsomal enzymes were embedded in an agar layer to prolong their viability, 1,1-bis(*p*-chlorophenyl)ethylene, a mammalian metabolite of 1,1-bis(*p*-chlorophenyl)-2, 2, 2-trichloroethane (DDT), was converted by microsomal monooxygenases of mouse liver into 1,1-bis(*p*-chlorophenyl)-1,2-ethanediol. The putative epoxide intermediate 1,1-bis(*p*-chlorophenyl)ethylene oxide, a new compound, was synthesized; it showed weak alkylating activity with 4-(4-nitrobenzyl)pyridine but was not mutagenic in *Salmonella typhimurium* strains TA100 and TA98. DDT and 13 of its metabolites or putative synthetic derivatives, including 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethylene, 1,1-bis(*p*-chlorophenyl)-2-chloroethylene, 1,1-bis(*p*-chlorophenyl)-2-chloroethane, 2,2-bis(*p*-chlorophenyl)ethanol, bis(*p*-chlorophenyl)acetic acid, and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol (Kelthane), caused no mutagenic effects in *S. typhimurium* strains TA100 or TA98, either in the presence or absence of a mouse-liver microsomal fraction. 1,1-Bis(*p*-chlorophenyl)-2,2,2-trichloroethyl acetate (Kelthane acetate) was a direct-acting mutagen in strain TA100, whereas 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane was mutagenic in TA98, only in the presence of a mouse-liver microsomal system. The results are discussed in relation to possible pathways whereby DDT is converted to mutagenic and/or carcinogenic metabolites. (48 refs)

79-5527 Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats. (Eng) Gehring, P. J. (Toxicology Res. Lab., Dow Chemical, Midland, MI 48640); Watanabe, P. G.; Park, C. N. *Toxicol Appl Pharmacol* 49(1): 15-21; 1979.

Dose-response data for the induction of angiosarcoma in rats exposed to various levels of vinyl chloride (VC) together with attendant biotransformation data were used to estimate the risk of developing angiosarcoma in persons exposed to VC. Since a biotransformation product of VC, not VC per se, is responsible for the induction of angiosarcoma, the body surface area of people relative to rats was used to estimate the dose of the carcinogen biotransformed from VC by the former. Four models were used to extrapolate the data. Using a probit model, 10 hepatic angiosarcomas were predicted to occur in a recently reported epidemiological cohort of 9,677 workers; in actuality, five have occurred. Linear models and a model based on the equation, Risk = $1 - e(-\beta x)$, where x = dose, do not appear as reliable. For an 8-hr day, 5 days/week, 35-year time-weighted-average exposure of 1 ppm, the predicted incidence of hepatic angiosarcoma using the probit model is 1.5×10^{-6} . (16 refs)

79-5528 Vinyl Chloride and Trichloroethylene: Comparison of Alkylating Effects of Metabolites and Induction of Preneoplastic Enzyme Deficiencies in Rat Liver. (Eng) Laib, R. J. (Institut für Toxikologie, Universität Tübingen, Wilhelmstrasse 74, D-7400 Tübingen, W. Germany); Stockle, G.; Bolt, H. M.;

Kunz, W. *J Cancer Res Clin Oncol* 94(2): 139-147; 1979.

The extent of alkylation of nucleic acid by metabolites of trichloroethylene (TCE) and vinyl chloride (VC) was compared, along with the induction, by TCE and VC, of preneoplastic foci deficient in nucleoside-5-triphosphatase in newborn Wistar rats. [$1,2-^{14}\text{C}$]VC and [$1,2-^{14}\text{C}$]TCE were incubated with rat liver microsomes, NADPH, and yeast RNA. TCE metabolites were irreversibly bound to proteins in microsomal incubations to a higher extent than VC metabolites, but irreversible binding to RNA was lower for TCE metabolites. Hydrolysis of the RNA that was reisolated from microsomal incubations with ^{14}C -VC or ^{14}C -TCE and separation of the nucleosides showed different alkylation products arising from VC and from TCE. 1,N⁶-Ethenoadenosine and 3,N⁴-ethenocytidine were produced only with metabolites of VC, possibly through the formation of an imidazol ring. The different reactivities of VC and TCE metabolites prompted a comparison of the oncogenic effects of both compounds in rat liver cells. Newborn rats were exposed for 10 wk to 2,000 ppm VC or TCE 8 hr/day, 5 days/wk. After this period, livers of the animals were stained for nucleoside-5-triphosphatase. The VC-exposed rats showed focal hepatocellular deficiencies in this enzyme, which are supposed to represent an early sign of malignancy; no such changes were induced by TCE exposure. The data therefore suggest differences between the activity of VC and TCE in the rat liver. (24 refs)

79-5529 The effects of 1,1-Di(*p*-chlorophenyl)-2-chloroethylene on Plasma Enzymes and Blood Constituents in the Japanese Quail. (Eng) Westlake, G. E. (Pest Infestation Control Lab., Ministry Agriculture, Fisheries and Food, Tolworth, Surbiton, Surrey, KT6 7NF, England); Bunyan, P. J.; Stanley, P. I.; Walker, C. H. *Chem Biol Interact* 25(2/3): 197-210; 1979.

Glutamate oxaloacetate transaminase (GOT), glutamate dehydrogenase (GDH), sorbitol dehydrogenase (SDH), pseudo-cholinesterase (ChE) and various blood constituents were measured in the plasma of Japanese quail fed 1,1-di(*p*-chlorophenyl)-2-chloroethylene (DDMU) at low levels (50, 100, and 150 ppm) for periods ranging from 2 to 32 days. Previous work has shown that DDMU is a potent inducer of hepatic microsomal enzymes causing marked structural changes in the liver. A rapid increase in plasma GOT was observed within 4 days, accompanied by an increase in relative liver weight. Plasma GDH and SDH increased to a maximum between 16 and 24 days, suggesting an association with hepatic cell proliferation. Plasma ChE showed a steady increase over the time course of DDMU administration. The level of plasma lipid was reduced after 4 days, whereas the hepatic lipid content was substantially increased; thus the fatty liver condition may be caused by decreased release of triglyceride from the liver. Plasma glucose was reduced at 8 days, but there was no evidence of a hyperglycemic state. The changes noted after 2 days of DDMU diet were confirmed by measurements on birds 18 hr after oral dosing with DDMU (20, 100, 350, and 1,000 mg/kg body wt). The study demonstrates the values of plasma enzyme measurements for the early detection of toxic effects and indicates that DDMU administration leads to extrahepatic effects in addition to those previously described in the liver. (34 refs)

79-5530 Sensitivity of Human Lymphocyte Chromosomes to Ethylenimine Derivatives at Different Periods During

Cell Culture. (Eng) Bochkov, N. P. (Inst. Medical Genetics, Kashirskoye Shosse 6a, 115478 Moscow, USSR); Yakovenko, K. N. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977.* Medical Research Council (Edinburgh, Scotland): 355 pp.; 290-299; 1978.

The dependence of chromosome aberration frequency in unstimulated cultures of human lymphocytes on the time of addition of four ethylenimine derivatives, phosphamide (60 µg/ml), thiophosphamide (20 and 30 µg/ml), dipine (40 µg/ml), and fotrin (40 µg/ml), was investigated. The four mutagens differed with respect to number of alkylating groups and number of active mutagenic centers. The chemicals were added to separate cultures every 4 hr from culture initiation (zero time) to 104 hr. The duration of exposure was 1 hr. The cells were harvested after 56-108 hr of culture. The mutagens were cytogenetically effective at all stages of the cell cycle. Max sensitivity was observed at 28-32 hr of culture, ie, 24-28 hr before harvesting, except for cultures exposed to dipin, in which sensitivity was practically constant from 0 to 32 hr. Thereafter, the sensitivity of the chromosomes to all the mutagens sharply decreased and reached a minimum at 48-52 hr. With thiophosphamide, the time of exposure vs effect curves had the same shape, independent of harvesting time, and they were described by a fourth-order polynomial. In contrast, the time of harvesting vs effect curves had essentially different shapes, depending upon the time of mutagen action. For assaying mutagenicity in terms of chromosome aberrations, consideration should be given to two indices of the mitotic cycle. The first indicates what mitotic cycle after stimulation the cell is in at the moment of exposure to a mutagen; the second is the mitotic cycle the cell is in at the moment of harvesting. (10 refs)

79-5531 Renal Carcinogenic and Nephrotoxic Effects of the Flame Retardant Tris(2,3-dibromopropyl) Phosphate in F344 Rats and (C57BL/6N x C3H/HeN)F₁ Mice. (Eng) Reznik, G. (Tumor Pathology Branch, Carcinogenesis Testing Program, NCI, NIH, Div. Cancer Cause and Prevention, Bethesda, MD 20014); Ward, J. M.; Hardisty, J. F.; Russfield, A. *J Natl Cancer Inst* 63(1): 205-212; 1979.

The pathology of the kidneys in rats and mice administered high and low dose of the flame retardant tris(2,3-dibromopropyl) phosphate (TBP) is described in detail. TBP was administered in the feed of 55 male and 55 female inbred F344 rats (100 or 50 ppm) rats and 50 male and 50 female (C57BL/6N x C3H/HeN)F₁ mice. (1,000 or 500 ppm). For each rodent type, 55 animals of each sex were used as controls. In treated male and female rats and mice, renal epithelial tumors developed at significant incidences. These tumors included renal tubular cell adenomas and carcinomas that developed from the proximal convoluted tubular epithelium. Among female mice and rats, hyperplasia and/or dysplasia of the proximal convoluted tubular epithelium with or without cystic dilatation of the tubules and increases in the size of cell nuclei were dose-dependent and recognized as preneoplastic and/or toxic lesions. The comparative histogenesis of renal tubular neoplasms is surveyed. (37 refs)

79-5532 Hepatic and Extrahepatic Induction of Drug-metabolizing Enzymes in Specific Pathogen Free and Germ Free Rats. (Eng) Hietanen, E. (Dept. Physiology, Univ. Kuopio, SF 70101 Kuopio 10, Finland); Pelkonen, K. *Gen Pharmacol* 10(3): 239-247; 1979.

The tissue-specific responses of drug-metabolizing enzymes to the enzyme inducers phenobarbital (PB) and 3-methylcholanthrene (3-MC) were studied in specific-pathogen-free (SPF) and germfree (GF) male Han-Wistar rats. Rats received 80 mg/kg/day PB ip for 5 days or 100 mg/kg/day 3-MC ip for 3 days; 24 hr after the last dose, they were sacrificed and liver, kidney, and intestinal tissue was analyzed. The activities of NADPH cytochrome c reductase (NCCR), aryl hydrocarbon hydroxylase (AHH), ethoxycoumarin O-deethylase, (ECOD), and uridine diphosphate-glucuronosyl-transferase (UGT) did not differ between SPF and GF rats in any of the tissues examined. Hepatic NCCR activity was slightly enhanced by PB in SPF and GF rats but somewhat decreased by 3-MC in SPF rats. NCCR activity in kidney and intestinal mucosa was unchanged by PB or 3-MC in all rats. AHH activity was not inducible by PB in SPF or GF rats in any tissue examined; 3-MC induced hepatic AHH activity 2.6- to 2.7-fold in both SPF and GF rats, kidney AHH activity 15.2- and 11.7-fold in SPF and GF rats, respectively, and intestinal mucosa AHH activity 5.2- and 6.7-fold in SPF and GF rats. Hepatic ECOD activity was slightly elevated but kidney ECOD activity was unaffected by PB in SPF and GF rats; 3-MC induced hepatic ECOD activity 1.9- and 4-fold (a significant difference) in SPF and GF rats, respectively, and kidney ECOD activity approx 5-fold in both SPF and GF rats. UGT activity was measured both in native and in trypsin-digested microsomes because of the latency of the enzyme. In native hepatic microsomes, UGT was induced slightly by PB but 1.6-fold by 3-MC in both rat groups. In native renal microsomes, only 3-MC caused a significant, although slight, UGT induction in SPF and GF rats. UGT was not inducible in the intestinal postmitochondrial supernatant in SPF or GF rats. In hepatic trypsin-digested microsomes, UGT activity was increased approx 10-fold by PB and 3-MC in SPF and GF rats, compared with the respective native microsomes, but renal trypsin-digested microsomes showed the same UGT activity as native renal microsomes in all cases. Hepatic cytochrome P-450 levels and p-nitroanisole O-demethylase activity were highest in SPF and GF rats following PB administration. (44 refs)

79-5533 Effects of Asbestos and Beryllium on Release of Alveolar Macrophage Enzymes. (Eng) Kang, K. Y. (Dept. Medicine, Tulane Univ. Sch. Medicine, New Orleans, LA); Bice, D.; D'Amato, R.; Ziskind, M.; Salvaggio, J. *Arch Environ Health* 34(3): 133-140; 1979.

The activities of β -N-acetylglucosaminidase, β -glucuronidase, and phosphohexose isomerase increased significantly in the culture medium but not in the mitochondrial fraction of rabbit alveolar macrophages exposed in vitro to asbestos, beryllium sulfate, and beryllium oxide. Asbestos and beryllium sulfate were highly cytotoxic for alveolar macrophages. (21 refs)

79-5534 Chronic Arsenic Poisoning, a Problem in Anesthetic Management. (Eng) Rees, I. (Dept. Anesthesiology, Mount Sinai Sch. Medicine, New York, NY 10029); Adelman, M.; Pratilas, V. *Anesthesiology* 51(1): 84-86; 1979.

A case report illustrating the anesthetic considerations in a 50-yr-old woman with chronic arsenic poisoning from taking daily doses of Fowler's soln for the treatment of psoriasis for 10 yr is presented. A further anesthetic problem in this case was previous tracheal resection for carcinoma due to the arsenism. The patient manifested a generalized neoplastic diathesis of the skin, with cancer formation following nonspecific injuries and numerous

keratoses and granulomatous lesions at the sites of previous injections. (7 refs)

- 79-5535 Changes in Vitamin A Conditioned Hamster Cheek Pouch Epithelium on Exposure to Commercial Shell Lime (Calcium Hydroxide) and Tobacco-II Ultrastructure. (Eng) Kandarkar, S. V. (Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012, India); Sirsat, S. M. *Indian J Cancer* 15(3): 14-20; 1978.

The effect of lime (commercial shell lime, prepared as a paste) and tobacco (prepared as a plug) on the hamster cheek pouch conditioned by exposure to vitamin A palmitate was studied. Most vitamin A control and all experimental animals showed a roughened cheek pouch mucosa that became more marked with exposure time. The mild hyperplasia seen in the control and solvent (olive oil)-treated tissues was considered normal and subsequent to the trauma of food storage. Epithelial hyperplasia, hyperortho- and parakeratosis, and mild edema occurred after prolonged exposure to vitamin A alone. These changes were enhanced after treatment of the pouches with lime and tobacco, suggesting that longer exposure to these substances might have resulted in malignancy. (30 refs)

- 79-5536 Inducibility of Chromosomal Aberrations by Metal Compounds in Cultured Mammalian Cells. (Eng) Umeda, M. (Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho, Minami-ku, Yokohama 232, Japan); Nishimura, M. *Mutat Res* 67(3): 221-229; 1979.

Various metal compounds were tested for their ability to induce chromosome aberrations in cultured FM3A cells from a C3H mouse mammary carcinoma. Chromosome aberrations were induced by the application of some Cr, Mn, and Ni compounds. Among the hexavalent Cr compounds, $K_2Cr_2O_7$ and CrO_3 induced high levels of aberrations, at rates that were similar for Cr-equivalent doses. The perchromate compounds were more efficient in producing chromosome aberrations than was a chromate compound, K_2CrO_4 . A trivalent Cr compound, $Cr_2(SO_4)_3$, was less toxic and failed to induce a demonstrable increase in chromosome aberrations. $KMnO_4$ induced aberrations, but at a low rate. As to Ni compounds, $NiCl_2$ and $(CH_3COO)_2Ni$ induced few aberrations. Administration of $K_2Ni(CN)_4$ induced only gaps. NiS induced a low but definite increase in chromosome aberrations. The rate of these aberrations increased with an increase in treatment time from 24 to 48 hr, indicating that there is a time-dependent increase in the hereditary toxicity of metal compounds. $CdCl_2$ and $HgCl_2$ were somewhat toxic, but they failed to induce chromosome aberrations. (23 refs)

- 79-5537 Chromosomal Aberrations and Sister-Chromatid Exchanges in Chinese Hamster Cells Treated In Vitro with Hexavalent Chromium Compounds. (Eng) Majone, F. (Inst. Animal Biology, Univ. Padova, Via Loredan 10, 35100 Padova, Italy); Levis, A. G. *Mutat Res* 67(3): 231-238; 1979.

Chinese hamster ovary (CHO) cells were treated in vitro for 30-39 hr with $K_2Cr_2O_7$ or $Na_2Cr_2O_7$ (0.1 to 1.0 μg of Cr^{6+} /ml) in medium containing bromodeoxyuridine (BUDr). Chromosome aberrations and sister-chromatid exchanges (SCE's) were scored on BUDr-labeled second division metaphases, collected at the end of treat-

ment and stained with Giemsa. Treatment with mitomycin C (0.009-0.030 μg /ml) was carried out as a control for the responsiveness of the cell system to chromosome damage. Both chromium compounds induced marked mitotic delays. Chromosome aberrations were increased about 10-fold by exposure to Cr^{6+} (1.0 μg /ml). The principal aberrations observed were single chromatid gaps, breaks, and interchanges, the frequencies of which increased proportionally with the concentration of chromium. Dicentric chromosomes, isochromatid breaks, and chromosome and chromatid rings were also induced. The frequency of SCE's was scarcely doubled 30 hr after exposure to 0.3 μg /ml Cr^{6+} whereas it was tripled 39 hr after treatment, in the cells whose mitotic cycle had been slowed by chromium. (20 refs)

- 79-5538 Histopathology of Neoplastic and Nonneoplastic Hepatic Lesions in Mice Fed Diets Containing Tetrachlorvinphos. (Eng) Ward, J. M. (Tumor Pathology Branch, Carcinogenesis Testing Program, Room 402, Del Ray Building, Bethesda, MD 20014); Bernal, E.; Buratto, B.; Goodman, D. G.; Strandberg, J. D.; Schueler, R. *J Natl Cancer Inst* 63(1): 111-118; 1979.

A morphological study was made of the hepatocellular carcinomas and unusual nonneoplastic lesions induced in mice by the organophosphorus insecticide tetrachlorvinphos. Tetrachlorvinphos was fed at 8,000 or 16,000 ppm in diets to male and female (C57BL/6N x C3H/HeN)F₁ mice for 80 wk. Surviving mice were killed at 92 wk, and all mice were completely necropsied. In the treated mice, there was a high incidence of unusual nonneoplastic hepatic lesions that were characterized by pericellular fibrosis, hepatocyte nuclear pleomorphism, and intrasinusoidal foci of macrophages with intracytoplasmic crystalline structures. From 84% to 94% of the treated male mice and from 21% to 23% of the treated females had hepatocellular neoplasms. Only 17% of the control males and 7% of the control females had liver tumors. The induced tumors were frequently multiple in the liver, whereas the tumors in the controls were usually singular. The morphology of 241 liver tumors in 110 treated mice was different from that of tumors in controls. Liver tumors in control mice were generally composed of small basophilic hepatocytes. In treated mice, the tumors were hepatocellular carcinomas composed of solid sheets of large basophilic or eosinophilic hepatocytes. Foci of prominent trabecular formation were seen in 51 tumors. Fifteen tumors were composed of small basophilic hepatocytes with oval cells interposed among them. Foci of capillary formation were noted in three of these tumors. In addition, seven more typical hemangiosarcomas in which sinusoids developed and in which thrombosis was frequent were observed. (25 refs)

- 79-5539 Intravesical thio-Tepa. A Study of ³H-Thymidine Uptake in Normal Urothelium and FANFT-induced Tumors in Rats. (Eng) Nieh, P. T. (Urological Service, Massachusetts General Hosp., Boston, MA 02114); Daly, J. J.; Irwin, R. J.; Prout, G. R. *Invest Urol* 16(6): 486-488; 1979.

The effect of the alkylating agent triethylenethiophosphoramide (thio-TEPA: 0.5 ml of a 4 mM soln given transurethrally) on the cell kinetics of normal and neoplastic female Fischer rat urothelium was studied. Half (27) of the weanling rats were pretreated with N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT: 0.188% in the diet for 6 mo), and they all developed gross papillary and sessile bladder tumors by age 9-12 mo. No bladder tumors were found in the 27 animals not exposed to

FANFT. At age 12-14 mo, intravesical instillations of thio-TEPA or saline were performed in all animals. Scintillation counting in both normal and tumorous urothelium exposed to thio-TEPA showed a bimodal pattern, with peaks of DNA synthesis occurring on days 3 and 9 after instillation. Activity in the urothelium of FANFT-treated animals 3 and 9 days after treatment with saline was 40 and 73 counts/min, respectively, compared with 423 ($p < 0.001$) and 437 counts/min ($p < 0.05$) at the same intervals after thio-TEPA treatment. In animals not pretreated with FANFT, counts after saline and thio-TEPA did not differ significantly. Radioautography confirmed these results. Repeat thio-TEPA instillation at 3 and 9 days might improve cytotoxicity and the overall response rate. (8 refs)

79-5540 Sister-Chromatid Exchanges in Human Lymphocytes Exposed During G_0 to Four Classes of DNA-Damaging Chemicals. (Eng) Littlefield, L. G. (Medical and Health Sciences Div., Oak Ridge Associated Univs., P.O. Box 117, Oak Ridge, TN 37830); Colyer, S. P.; Sayer, A. M.; Dufraim, R. J. *Mutat Res* 67(3): 259-269; 1979.

The effectiveness of clastogenic chemicals with different modes of action on DNA in inducing DNA lesions in G_0 lymphocytes that can subsequently be detected as sister-chromatid exchanges (SCE's) was evaluated. Human lymphocytes were treated prior to mitogenic stimulation with varying concentrations of six cytostatic drugs representing four classes of DNA-damaging chemicals. Afterward, the cells were washed to remove residual chemical and cultured in the presence of bromodeoxyuridine (BUdR) for analysis of SCE's. A dose-related increase in SCE's was observed in cells exposed during G_0 to the alkylating chemicals mitomycin C, chlorambucil, and thio-TEPA, but significant increases in SCE's were not noted in cultures exposed to methotrexate, cytarabine, or bleomycin. These findings suggest that not all classes of clastogenic chemicals that induce SCE's in proliferative cells substituted with BUdR are capable of inducing long-lived lesions in the DNA of G_0 lymphocytes that can lead to SCE formation. (40 refs)

79-5541 Platinum(II) Complexes Generate Frame-Shift Mutations in Test Strains of *Salmonella typhimurium*. (Eng) Andersen, K. S. (Inst. Life Sciences and Chemistry, Roskilde Univ., P.O.B. 260, DK 4000 Roskilde, Denmark). *Mutat Res* 67(3): 209-214; 1979.

In the *Salmonella typhimurium* mutagenicity assay, cis-diamminodichloroplatinum(II) (cis-PDD: 2.0 $\mu\text{g}/\text{plate}$) and diaquoethylenediamineplatinum(II) (411 $\mu\text{g}/\text{plate}$) induced histidine revertants in strains TA98 (frameshift mutation) and TA100 (base-pair-substitution mutation). A linear dose-response relationship was found with cis-PDD. *S. typhimurium* strains TA1535, TA1537, and TA1538 were not sensitive to the mutagenic action of cis-PDD. All five strains were sensitive to the toxic effect of cis-PDD. It is concluded that platinum(II) complexes induce mutations (frameshift or base-pair-substitution) only in strains carrying the R-factor plasmid. (12 refs)

79-5542 Mutagenicity, Cytotoxicity and DNA Crosslinking in V79 Chinese Hamster Cells Treated with *cis*- and *trans*-Pt(II) Diamminedichloride. (Eng) Zwelling, L. A. (Lab. Molecular Pharmacology, Div. Cancer Treatment, NCI, NIH,

Bethesda, MD 20014); Bradley, M. O.; Sharkey, N. A.; Anderson, T.; Kohn, K. W. *Mutat Res* 67(3): 271-280; 1979.

The mutagenicity and cytotoxicity of *cis*- and *trans*-platinum(II) diammine dichloride (PDD) were examined in V79 Chinese hamster lung cells, and the results were compared with the effects of these compounds on DNA, as measured by alkaline elution. DNA-protein crosslinks and DNA interstrand crosslinks were detected following doses of *cis*-PDD (10 μM) that reduced cell survival 80%-90% and produced a mutant frequency of 3×10^{-4} at the hypoxanthine-guanine phosphoribosyltransferase locus. Equitoxic doses of *trans*-PDD (320 μM) were much less mutagenic than *cis*-PDD. The *trans*-isomer produced little or no mutagenesis at concentrations up to 600 μM (<1% survival). At equitoxic doses, *trans*-PDD produced more DNA-protein crosslinking than did *cis*-PDD, but interstrand crosslinking for the two isomers was comparable. Hence, the interstrand crosslink could be the cytotoxic lesion produced by these Pt compounds. Neither of these DNA lesions are necessarily mutagenic. The mutagenesis produced by *cis*-PDD could be due to crosslinks of a different type than those produced by *trans*-PDD, or it may be due to monofunctional change. (29 refs)

79-5543 Mutagenic Activity of Sodium Bisulphite in Barley. (Eng) Kak, S. N. (Regional Res. Lab., Jammu Tawi, India); Kaul, B. L. *Experientia* 35(6): 739; 1979.

Hordeum vulgare was used as a test system for the mutagenic activity of sodium bisulfite (7 and 10 mM at 30 C for 6 hr). Both seedling injury and chlorophyll mutations indicated that the compound was highly mutagenic. (9 refs)

79-5544 Cycloheximide Inhibition of Hormonal Induction of α_{2u} -Globulin mRNA. (Eng) Chen, C. L. (Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY 10032); Feigelson, P. *Proc Natl Acad Sci USA* 76(6): 2669-2673; 1979.

Glucocorticoids induce hepatic α_{2u} -globulin (α_{2u} -G) synthesis in isolated hepatocytes by increasing the level of its messenger RNA (mRNA), as measured by cell-free translation and by hybridization to an α_{2u} -G complementary DNA probe. To explore whether the induction of this mRNA is a direct or an indirect consequence of the interaction of the dexamethasone-receptor complex with the α_{2u} -G genome, the requirement for ongoing protein synthesis was examined. A concentration of cycloheximide (0.05 $\mu\text{g}/\text{ml}$) too low to prevent precursor incorporation into total poly(A)-containing RNA prevented the hormonal induction of α_{2u} -G mRNA. Furthermore, incorporation of ^3H -labeled amino acids into total protein was decreased by only 40%-50%, and the appearance of the dexamethasone-induced glycosylated forms of α_{2u} -G was completely prevented in these cycloheximide-treated hepatocytes. The results suggest that the synthesis of a protein mediator(s) may be required for the induction of α_{2u} -G mRNA by glucocorticoids and that the steroid-receptor complex may not interact directly with the α_{2u} -G genome. (27 refs)

79-5545 Acute Toxicity of Methyl Fluorosulfonate (Magic Methyl). (Eng) Hite, M. (Merck Inst. Therapeutic Res., Merck Sharp & Dohme Res. Lab., West Point, PA 19486); Rinehart, W.; Braun, W.; Peck, H. *Am Ind Hyg Assoc J* 40(7): 600-603; 1979.

The po LD₅₀ of methyl fluorosulfonate was estimated to be less than 112 mg/kg in mice. The LC₅₀ for a 1-hr exposure to the vapors of this compound was approximately 0.025-0.029 mg/liter (5-6 ppm) in rats. The compound was severely irritating to the eyes in rabbits and produced toxic signs and death when administered by this route. Methyl fluorosulfonate was also corrosive to the skin and was lethal at a dose of 455-614 mg/kg in rabbits. (5 refs)

79-5546 Carcinogenic N-Nitrosodimethylamine as a Contaminant in Drugs Containing 4-Dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (Amidopyrine, Aminophenazone). (Eng) Eisenbrand, G. (Deutsches Krebs-Forschungszentrum, Institut für Toxikologie und Chemotherapie, Postfach 10 19 49, Heidelberg, W. Germany); Spiegelhalter, B.; Kann, J.; Klein, R.; Preussmann, R. *Arzneim Forsch* 29(6): 867-869; 1979.

Sixty-eight commercially available drugs containing amidopyrine (AP) were analyzed for possible contamination by the strong carcinogen N-nitrosodimethylamine (NDMA), which can be produced from AP under nitrosating conditions. All drugs contained 1-370 μ g/kg NDMA, 51% containing 1-10 μ g/kg and 40% containing 11-50 μ g/kg. Large variations in NDMA content were found on repeat analyses of the same samples and of pure AP. Exposure of tablets containing 300 mg AP and 160 mg ascorbic acid to 100 ppm NO₂ resulted in increases in NDMA content from 78 μ g/kg to 20,200 μ g/kg within 12 hr. Exposure of similar tablets to 1 ppm NO₂ for 12 hr increased the NDMA content to 5,090 μ g/kg. After 2 and 4 hr exposure to 1 ppm NO₂, the NDMA content increased from 100-180 μ g/kg to 440-510 μ g/kg and 750-800 μ g/kg, respectively. The ascorbic acid content of the tablets did not significantly affect the NDMA content. (9 refs)

79-5547 Demonstration of Effective Antitumor Immunity in an Autochthonous Host Bearing Primary Colon Tumors Induced by 1,2-Dimethylhydrazine Dihydrochloride. (Eng) Bansal, B. R. (Dept. Surgery, Alma Dea Morani Lab. Surgical Immunobiology, Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA 19129); Mark, R.; Mobini, J.; Rhoads, J. E.; Bansal, S. C. *J Natl Cancer Inst* 63(1): 127-132; 1979.

The effectiveness of host antitumor immunity induced by the primary tumor against nascent tumors in an autochthonous host was examined in a model rat colon carcinoma induced by 1,2-dimethylhydrazine dihydrochloride (DMH). Inbred WF female rats received DMH sc at a dose of 15 mg/kg/wk in two divided doses from 58 to 112 days of age. Tumors were diagnosed at laparotomy, and sequential laparotomies were done at 30-day intervals. In Group 1 (control), all tumors were left in situ. In Group 2 (control), the first tumor(s) in each rat was isolated from the GI tract (the continuity of which was reestablished) and left in situ for continuous growth in the isolated segment of the colon. In Group 3 (immune), the first tumor(s) in each rat was excised and the continuity of the colon reestablished. In Group 4 (immune), tumors were handled as in Group 3 and the rats received antithymocyte globulin (ATG: 10 mg/kg for 5 days) 7 days after the excision. Excision of the first tumor appeared to induce specific antitumor immune responses, because only 2 additional tumors were observed in the 10 Group 3 rats after excision of the first tumors, whereas 13 and 12 additional tumors were observed in 10 and 9 rats in Groups 1 and 2, respectively, after diagnosis or isolation of the first tumors. Immunosuppression with ATG decreased the effectiveness of the antitumor immunity induced by first tumor exci-

sion, as 7 additional tumors were observed in 10 Group 4 rats. These results suggest that an effective antitumor immunity is induced against successive tumors of an organ after complete excision of a tumor originating in the same organ. The findings are discussed in relation to observations of multiple primary neoplasms in humans. (31 refs)

79-5548 Angiosarcoma of Liver Associated with Phenelzine. (Eng) Daneshmend, T. K. (Bristol Royal Infirmary, Bristol BS2 8HW, England); Scott, G. L.; Bradfield, J. W. *Br Med J* 1(6179): 1679; 1979.

A case of liver angiosarcoma in a woman who had taken phenelzine for at least 6 yr (45 mg/day for the first 3 yr, 15 mg/day thereafter) is reported. There was no history of exposure to thorium dioxide, arsenic, or vinyl chloride. An osteolytic area suggestive of metastatic disease was present in the lateral epicondyle of the right humerus. Phenelzine administration increases the incidence of angiosarcoma in female mice, suggesting a possible etiologic relationship in this patient. (4 refs)

79-5549 Hepatocarcinogenesis by Hydrazine Mycotoxins of Edible Mushrooms. (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE). *J Toxicol Environ Health* 5(2/3): 193-202; 1979.

The tumorigenicity of the hydrazine compounds found in two types of edible mushrooms was determined in Swiss mice and Syrian golden hamsters. The wild false morel *Gyromitra esculenta* contains up to 0.3% acetaldehyde methylformylhydrazine and N-methyl-N-formylhydrazine (MFH). The latter chemical, under certain conditions, also yields methylhydrazine. The cultivated mushroom *Agaricus bisporus* contains up to 0.04% β -N-[γ -L-(+)-glutamyl]-4-hydroxymethylphenylhydrazine and 4-hydroxymethylphenylhydrazine (HMPH). MFH (0.0156%-0.001%) was administered in the drinking water of the mice and hamsters continuously, over their life-spans. In both species, the compound induced high incidences of benign and malignant hepatocellular neoplasms. Also, methylhydrazine given in the drinking water (0.01%) induced a significant incidence of malignant histiocytomas in the livers of hamsters. The N'-acetyl derivative of HMPH administered po to mice (0.0625% in the drinking water) gave rise to lung tumors and blood vessel tumors, mainly in the liver. Furthermore, all three compounds produced tumors in various other tissues. Histopathologically, the tumors were classified as benign hepatomas, liver cell carcinomas, angiomas and angiosarcomas of the blood vessels, and adenomas and adenocarcinomas of the lungs. Since mushrooms containing these hydrazine analogs are consumed on a large scale by humans in various parts of the world, their hazardous nature should be considered. (38 refs)

79-5550 Dependence of Tumor Spectrum on Route of Administration in Sprague-Dawley Rats as a Result of Single or Multiple Injections of Methyl(acetoxymethyl)nitrosamine. (Eng) Berman, J. J. (Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20205); Rice, J. M.; Wenk, M. L.; Roller, P. P. *J Natl Cancer Inst* 63(1): 93-100; 1979.

The effect of route and schedule of administration of

methyl(acetoxymethyl)nitrosamine (DMN-OAc) to 5-wk-old Sprague-Dawley rats on the tumor spectrum was determined. Sixty females and 361 males were divided into treatment groups of 30 rats; male and female rats received single ip treatments [0.1 millimole (mmol)/kg body wt]; male rats received multiple ip treatments (0.02 or 0.04 mmol/kg x 5), single po or iv treatments (0.1 mmol/kg), or single (0.1 mmol/kg) or multiple (0.02 or 0.04 mmol/kg x 5) sc treatments. The single ip injections induced a high yield of intestinal tract epithelial tumors, particularly in males: 70 tumors were observed in 29 males and 41 tumors in 29 females. Five doses of 0.02 mmol/kg yielded only 51 intestinal tumors in 30 males, but five doses of 0.04 mmol/kg yielded 168 intestinal tumors in 29 males. A significant incidence of nervous system tumors, principally schwannomas arising from small nerves in the serosae of abdominal organs, occurred in rats treated ip with DMN-OAc. Numerous other tumors were found, but not at significant incidences compared with controls. Treatment by routes other than ip virtually eliminated the selectivity of DMN-OAc for the intestines and produced high yields of other tumor types. The single po treatments produced a high yield of stomach tumors (31 and 39 tumors in 2 groups of 30 rats, respectively), mostly adenocarcinomas. The single iv injection yielded 42 lung tumors, 9 Zymbal's gland tumors, and 8 endocardial neurinomas in 31 rats. Single and multiple sc treatments produced a high incidence of mammary tumors 5/30, 7/30, 9/29, soft tissue tumors at the injection site (9/30, 15/30, 15/29), and lung tumors (32/30, 6/30, 32/29, respectively). (13 refs)

79-5551 Metabolism and Activation of 2-Acetylaminofluorene in Isolated Rat Hepatocytes. (Eng) Dybing, E. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); Soderlund, E.; Haug, L. T.; Thorgeirsson, S. S. *Cancer Res* 39(8): 3268-3275; 1979.

The metabolism of 2-acetylaminofluorene (AAF) and its activation to covalently bound and mutagenic intermediates were studied in isolated male Wistar rat hepatocytes. The cell system readily formed oxidized, deacetylated, and conjugated AAF metabolites. Pretreatment of animals with the inducer β -naphthoflavone led to increases in phenolic and conjugated as well as covalently protein-bound products. Addition of 4-nitrophenol, a substrate for conjugation, increased the levels of free phenols and inhibited the formation of water-soluble metabolites. At the same time, the rates of covalent protein binding were decreased. Formation of 9-hydroxy-2-acetylaminofluorene could also be demonstrated. The pathway leading to this alicyclic hydroxylated AAF metabolite was not induced by prior β -naphthoflavone treatment, nor was it inhibited by 4-nitrophenol addition. The cell system converted AAF as well as 2-aminofluorene and 2,4-diaminoanisole to mutagenic intermediates that were released into the incubation medium. 2-Aminofluorene was considerably more mutagenic than AAF in this system. Addition of microsomes increased the mutagenicity of AAF, but not that of 2-aminofluorene or 2,4-diaminoanisole, presumably by deacetylation of N-hydroxy-2-acetylaminofluorene to N-hydroxy-2-aminofluorene. (52 refs)

79-5552 The Early Effects of Chemical Carcinogens on Adult Rat Hepatocytes in Primary Culture. II. Effects on Unscheduled DNA Synthesis, Cell Division and α -Fetoprotein Production. (Eng) Lowing, R. K. (Health and Safety Executive, Cricklewood, London, England); Fry, J. R.; King, L. J.; Bridges, J. W. *Chem Biol Interact* 25(2/3): 303-319; 1979.

Rat hepatocytes in primary maintenance culture were exposed for 3 hr to a number of carcinogens and noncarcinogens and then studied with respect to cytotoxicity and alterations in mitotic index (MI), unscheduled DNA synthesis (UDS), and α -fetoprotein (AFP) production. The carcinogens tested were 3-methylcholanthrene (3-MC), 2-acetylaminofluorene 2-AAF, 3'-methyl-2-dimethylaminoazobenzene (3'-Me-DAB), and 6-aminochrysene (6-AC), and the noncarcinogens were 2-methyl-DAB and 2-AC. All compounds were cytotoxic at concentrations of 0.1-100 μ M. The carcinogens increased the MI and UDS in cultured hepatocytes, but cytotoxic concentrations of the noncarcinogens did not. 3-MC, 2-AAF, and 6-AC also caused the appearance of AFP in the treated cells, whereas 2-AC did not; AFP was also not detected in untreated cells. The changes in MI, UDS, and AFP production occurred above the background of cytotoxicity. Cytotoxicity, and the increases in MI and UDS were dose-dependent phenomena. The AFP production was transient, commencing approx 24 hr after cessation of exposure and becoming undetectable approx 84 hr after cessation of exposure. The time course of appearance of the increase in MI and AFP production were similar after 3-MC exposure, with the former occurring slightly before the latter, which suggests that AFP production depends on the generation of a cell species functionally distinct from nondividing hepatocytes. The parameters measured in these assays may be useful as part of a screening program for chemical carcinogens. (49 refs)

79-5553 Effects of Piperonyl Butoxide on the Toxicity and Hepatocarcinogenicity of 2-Acetylaminofluorene and 4-Acetylaminobiphenyl, and Their N-Hydroxylated Derivatives, Following Administration to Newborn Mice. (Eng) Fujii, K. (Dept. Pathology, Sch. Medicine, Univ. Tsukuba, Ibaraki, Japan); Epstein, S. S. *Oncology* 36(3): 105-112; 1979.

Studies were conducted to determine whether microsomal enzyme inhibition induced by piperonyl butoxide (PiB) modifies the toxic and carcinogenic effects of 2-acetylaminofluorene (AAF), 4-acetylaminobiphenyl (AAB), and their N-hydroxylated derivatives. Neonatal ICR/Ha mice were injected sc with a single dose of 25, 50, or 100 μ g of AAB, N-hydroxy-4-acetylaminobiphenyl (N-OH-AAB), AAF, or N-hydroxy-2-acetylaminofluorene (N-OH-AAF), alone or together with 2.5% PiB in tricaprillin. Negative control groups were injected with tricaprillin, and positive control groups were injected with 30 μ g of 7,12-dimethylbenz(a)anthracene (DMBA), alone or with PiB. PiB induced synergistic toxicity in the various groups of mice injected with the nonhydroxylated and hydroxylated amine carcinogens or with DMBA, compared with groups injected with carcinogen alone. AAB, N-OH-AAB, AAF, and N-OH-AAF induced dose-related hepatocarcinogenicity in male, but not female, mice, and this effect was not consistently influenced by concomitant administration of PiB. DMBA induced pulmonary adenomas and lymphomas in both sexes and hepatomas in males, and the incidences of these tumors were not modified by PiB. (16 refs)

79-5554 Reactions of the Carcinogen N-Acetoxy-4-acetamidostilbene with Nucleosides. (Eng) Scribner, N. K. (Pacific Northwest Res. Foundation, 1102 Columbia St., Seattle, WA 98104); Scribner, J. D.; Smith, D. L.; Schram, K. H.; McCloskey, J. A. *Chem Biol Interact* 26(1): 27-46; 1979.

Reaction of the carcinogen N-acetoxy-4-acetamidostilbene (N-AcO-AAS) with guanosine, adenosine, or cytidine in aqueous

CHEMICAL CARCINOGENESIS

acetone yielded multiple products. The major product from the reaction with cytidine was a deamination product, 1-(4-acetamidophenyl)-1-(3-uridyl)-2-hydroxy-2-phenylethane. Three minor products were unstable and were characterized only by their UV spectra and pK values. Adenosine yielded two major products, 1-(4-acetamidophenyl)-1-(N⁶-adenosyl)-2-hydroxy-2-phenylethane and 3-(β-D-ribose)-7-phenyl-8-(4-acetamidophenyl)-7,8-dihydroimidazo[2,1-i]purine. The major adduct with guanosine was 1-(4-acetamidophenyl)-1-(1-guanosyl)-2-hydroxy-2-phenylethane. One minor adduct also appeared to be a guanosine-N-1 derivative; two other minor adducts yielded 1-(4-acetamidophenyl)-2-phenyl-1,2-ethanediol on acid hydrolysis and, thus, appeared to be O⁶-derivatives. None of the guanine adducts isolated had the properties of N-7, C-8, or N² adducts. In this respect, N-Aco-AAS appeared to behave more like a classical alkylating agent than like the previously studied N-acetoxy-N-arylacetamides, although the target organs of 4-acetamidostilbene were the same as those of other N-arylacetamides. (34 refs)

- 79-5555 Reactions of the Carcinogen N-Acetoxy-4-acetamidostilbene with Polynucleotides In Vitro. (Eng) Scribner, N. K. (Pacific Northwest Res. Foundation, 1102 Columbia St., Seattle, WA 98104); Scribner, J. D. *Chem Biol Interact* 26(1): 47-55; 1979.

The in vitro reactions of N-Acetoxy-4-acetamidostilbene (N-Aco-AAS) with homopolynucleotides, RNA, and DNA are described. Homopolynucleotides, RNA, and DNA were treated with N-[β-¹⁴C]-Aco-AAS, washed, degraded with S₁ nuclease and acid phosphatase, and chromatographed on Sephadex LH-20. RNA prepared in vitro with ¹⁴C on cytosine, adenine, or guanine was treated with nonradioactive N-Aco-AAS and then digested and chromatographed similarly. By this means, many of the adducts arising from nucleoside reactions were shown to result from the treatment of nucleic acids with the same carcinogen; in addition, several products that have not been matched to products of monomer alkylation also resulted. Labeled 1-(4-acetamidophenyl)-2-phenyl-1,2-ethanediol was detected in the digest of RNA treated with radioactive N-Aco-AAS, which suggests that phosphate alkylation had taken place. (13 refs)

- 79-5556 Microsomal Metabolism of Arylamides by the Rat and Guinea Pig - II. Oxidation of 3-Fluorenyl acetamide at Carbon Atom 9 Formation of 3-Acetamido-9-Fluorenone. (Eng) Kaplan, E. (Lab. Cancer Res., Veterans Admin. Hosp., Minneapolis, MN 55417); Gutmann, H. R. *Biochem Pharmacol* 28(10): 1609-1614; 1979.

The formation of 9-hydroxy-3-fluorenylacetamide (9-hydroxy-3-FAA) from N-3-fluorenylacetamide (3-FAA) was examined in order to ascertain whether the formation of the ketone 3-acetamido-9-fluorenone (9-oxo-3-FAA8) is catalyzed by the same enzyme(s). In addition, the intracellular distribution of the microsomal enzyme(s) involved in the formation of 9-oxo-3-FAA and of 9-hydroxy-3-FAA was investigated. Two pathways are theoretically possible for the formation of 9-oxo-3-FAA from 3-FAA: it could arise from 3-FAA by way of the intermediate, 9-hydroxy-3-FAA, or the arylamide could yield the ketone by an oxidative mechanism at Carbon 9 (C-9) not involving the intermediate formation of the alcohol. Data is presented which demonstrates that although both reactions are oxidative, the marked differences in the cofactor requirements for hydroxylation of 3-FAA and for oxidation of 9-hydroxy-3-FAA indicated that the two

reactions are catalyzed by different enzymes. It was previously shown that CO inhibits the hydroxylation of 3-FAA at C-9 by 70%-80%. No inhibitory effect of CO was observed on the dehydrogenation of 9-hydroxy-3-FAA to 9-oxo-3-FAA. This, plus results of studies concerning pH changes, led to the conclusion that the subsequent oxidation of the alcohol to the ketone is not catalyzed by a microsomal heme protein and that the two oxidative reactions are attributable to two separate enzymes. Final evidence for two distinct enzymes came from the determination of the intracellular distribution of the hydroxylating and of the dehydrogenating activities. While 85%-90% of the hydroxylating activity was concentrated in the microsomal fraction, the dehydrogenating activity was approx equally distributed between the microsomal and the soluble fractions. The ketone-forming enzyme utilized NADP⁺ and NAD⁺ and did not appear to be a heme protein, in contrast to the alcohol-forming enzyme. (15 refs)

- 79-5557 Nitrous Acid Mutagenesis of Duplex DNA as a Three-Component System. (Eng) Thomas, H. F. (Dept. Medical Genetics, Univ. Wisconsin, Madison, WI 53706); Hartman, P. E.; Mudryj, M.; Brown, D. L. *Mutat Res* 61(2): 129-151; 1979.

The effect of nitrosation of a variety of compounds on the mutagenesis of duplex DNA by nitrous acid (NA) was studied. Denatured DNA from *Hemophilus influenzae* was readily mutated by NA to give kanamycin-resistant (KR) and erythromycin-resistant (ER) mutants. The low linear rate of induction of ER mutants with NA alone was increased when putrescine or phenol was present in the reaction mixture. There was a requirement for continuous generation of nitrosophenol for optimal mutagenesis. Using KR as a selective marker, NA was mutagenic for native DNA only when one of the four common polyamines was added to the reaction mixture. The method of DNA preparation was important in ensuring freedom from low-mol-wt molecules capable of enhancing NA mutagenesis of native DNA. Appreciable stimulation of the production of KR mutants occurred when 0.02-0.2 mM spermine was present in the reaction mixture, and, at a standard spermine concentration, the rate of mutation induction to KR increased with increasing concentrations of NaNO₂. The rate of NA mutagenesis in the presence of spermine was also a function of pH (optimum, 4.5-4.6). A variety of diamines, alcohols, and glycols was able to promote NA mutagenesis. The half-life of the spermine reaction product was about 4 min. NA reaction mixtures containing spermine or ethanol possessed greater mutagenic activity for *Salmonella typhimurium* than did NA alone. Spermine specifically enhanced the reversion of a base-substitution mutation and had no stimulatory effect on the reversion of frameshift mutations. All three *Escherichia coli* loci were susceptible to NA mutagenesis, but the addition of polyamine enhanced only the frequency of base-substitution mutations. (92 refs)

- 79-5558 Inhibition of N-n-Butyl-N-(4-hydroxybutyl) nitrosamine-induced Urinary Bladder Cancer in Rats by Administration of Disulfiram in the Diet. (Eng) Irving, C. C. (Veterans Admin. Medical Center, 1030 Jefferson Ave., Memphis, TN 38104); Tice, A. J.; Murphy, W. M. *Cancer Res* 39(8): 3040-3043; 1979.

The effect of disulfiram (Ds) on the induction of urinary bladder cancer in rats given N-n-butyl-N-(4-hydroxybutyl) nitrosamine (BHN) was examined. Adult male Wistar rats were divided into four groups: (1) control diet, 30 rats; (2) control diet plus 0.025%

BHBN in the drinking water, 60 rats; (3) control diet containing 0.5% DS, 30 rats; and (4) control diet containing 0.5% DS plus 0.025% BHBN in the drinking water, 60 rats. The animals were kept on these regimens for 15 wk and then were transferred to and maintained on the control diet. The av total intake of BHBN was 1.21 g/rat for Group 2 and 1.23 g/rat for Group 4. The cumulative incidences of bladder cancer at 25 wk after initial exposure to BHBN were: Group 1, 0/9; Group 2, 27/27; Group 3, 0/9; and Group 4, 0/27. At the end of the experiment (32-42 wk), the final bladder cancer incidences were: Group 1, 0/30; Group 2, 57/57; Group 3, 0/24; and Group 4, 7/55. Except for a carcinoma of the renal pelvis in one rat in Group 2 and the bladder tumors in Groups 2 and 4, tumors were not detected in other organs of any of these rats. It was concluded that DS significantly inhibited the induction of bladder cancer in rats exposed to BHBN. The mechanism of action of DS in this process is being investigated. (24 refs)

79-5559 Dose-dependent DNA Ruptures Induced by the Procarcinogen Dimethylnitrosamine on Primary Rat Liver Cultures. (Eng) Mendoza-Figueroa, T. (Departamento de Biología Celular, Centro de Investigación y de Estudios Avanzados del IPN, Ap. Postal 14-740 Mexico City 14, Mexico); Lopez-Revilla, R.; Villa-Trevino, S. *Cancer Res* 39(8): 3254-3257; 1979.

The amount of breakage produced by dimethylnitrosamine (DMN) in the DNA of primary male Wistar rat liver cultures was measured. Rat liver cells were isolated 20-24 hr after partial hepatectomy, cultured, and pulse-labeled in vitro with [³H]thymidine. Radioactively labeled cultures were treated with DMN or with the direct carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and then lysed directly onto alkaline sucrose gradients. DMN and MNNG caused a dose-dependent reduction in the mol wt of the DNA, and MNNG was approx 1,000 times more potent than DMN. DNA breaks appeared to be carcinogen-specific and not due to cell death, since treatment with high doses of cycloheximide, a noncarcinogenic hepatotoxic agent, was without significant effect. The data indicate that detection of DNA breaks constitutes a more sensitive assay of DMN effects than determination of unscheduled DNA synthesis in primary liver cultures. Quantitation of DNA breaks in liver cells may have value as a short-term assay for the identification of possible carcinogens and procarcinogens. (22 refs)

79-5560 Importance of Hepatic Neoplasms in Lower Vertebrate Animals as a Tool in Cancer Research. (Eng) Ishikawa, T. (Dept. Experimental Pathology, Cancer Inst., Tokyo, Japan); Takayama, S. *J Toxicol Environ Health* 5(2/3): 537-550; 1979.

The histological and autoradiographic findings are reported on hepatic tumors induced in medakas (*Oryzias latipes*) by the addition of diethylnitrosamine (DEN) to their aquarium water, and the effect of the length of carcinogen exposure on tumor incidence is discussed. The tanks were kept in incubators at temperatures of 25 C or 18 C. At 25 C, water-soluble DEN was added to the water at concentrations of 15, 30 or 45 ppm for 8 wk. At 18 C, a single dose of DEN (45 ppm) was added for 8 wk, after which the fish were maintained in normal water at 18 C for 6 more wk. Fish were selected randomly from each group at weekly or biweekly intervals and studied using light microscopy. Autoradiographic studies were conducted on 5 fish in the group treated with 30 ppm DEN weekly throughout the 8-wk experimental period. To investigate the effect

of DEN exposure period on the incidence of liver tumors, ten tanks of fish were exposed to a single dose of DEN (45 ppm) for 3 days or 1, 2, 4, or 6 wk at 25 C, after which time the fish were maintained in normal water. At the end of 13 wk, the survivors were killed and their liver tumor incidence determined. Liver tumors appeared as early as 5 wk after the beginning of treatment with DEN, and most of the fish treated with high concentrations had tumors by 6-8 wk. Multiple bizarre, basophilic cell foci arose among degenerating parenchymal cells after 4-5 wk treatment with DEN. The bizarre cells appeared to be resistant to the toxicity of DEN and were shown to be highly proliferative by autoradiography. Tumor incidence increased in proportion to the exposure period, and exposure to 45 ppm DEN for 2 wk was required for tumor development at 13 wk. At lower temperatures, the tumors were found in 1/3 fish at 8 wk; and the tumors were smaller than those observed at 25 C, even after 12-14 wk treatment. The use of these fish in carcinogenic studies is discussed. (30 refs)

79-5561 Changes in the Labeling Index and DNA Content of Liver Cells During Diethylnitrosamine-induced Liver Tumorigenesis in *Oryzias latipes*. (Eng) Kyono, Y. (Zoological Inst., Faculty Science, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan); Shima, A.; Egami, N. *J Natl Cancer Inst* 63(1): 71-74; 1979.

Changes in DNA synthesis and DNA levels in liver cells during diethylnitrosamine (DENA)-induced hepatocarcinogenesis in medaka fish (*Oryzias latipes*) were measured by autoradiography and Feulgen-DNA cytofluorometry. The fish were kept for 6 wk in water containing DENA (100 ppm). A single pulse of 1 μ Ci ³H-thymidine was given ip to each fish 2 hr before sacrifice, and the labeling indices of five to seven fish were counted throughout the 13 wk of the experiment. After 1 wk, the indices in both parenchymal and nonparenchymal cells were at control levels, but they increased rapidly at 2 wk and stayed high during DENA treatment. However, the indices decreased immediately after the fish were transferred into water without DENA. Tumor nodules of various sizes were observed at 11-13 wk. The labeling index in the basophilic hyperbasophilic cells in these nodules was increased, but the indices in the parenchymal and nonparenchymal cells fell to control levels at 11-13 wk. Parallel with histologic studies, the nuclear DNA level of each hepatocyte was measured by Feulgen-DNA cytofluorometry and autoradiography. DNA levels, became widely distributed even before appreciable histologic changes could be detected. During treatment of the fish with DENA, DNA levels in the labeled hepatocytes ranged from the normal diploid of 2C to >6C. When the tumor nodules were studied histologically, the DNA distribution histogram was found to be similar to that of controls except for the presence of hepatocytes with higher DNA levels (around 6C). (16 refs)

79-5562 Effect of Diethylnitrosamine on the Rat Liver Protein-synthesizing System. (Rus) Osipova, L. A. (Dept. Simulation Tumor Process, Inst. Oncological Problems, Kiev, USSR); Grinchishin, V. P. *Vopr Onkol* 25(6): 54-59; 1979.

The effect of a single dose of diethylnitrosamine (DENA) on rat liver protein synthesis was evaluated in random-bred albino rats. Animals were subjected to partial hepatectomy and, 24 hr later, inoculated ip with DENA (0.05% soln, 1 ml/100 g). The rats were sacrificed at various times after surgery, and the level of free and membrane-bound polyribosomes, as well as the rate of incorporation of messenger RNA (mRNA) into both types of

polyribosomes, were determined. The single injection of DENA caused a significant decrease in the amount of membrane-bound polyribosomes on days 4-5 and 21-28 after hepatectomy. DENA also inhibited the hepatectomy-induced increase of mRNA incorporation into both free and membrane-bound polyribosomes. (13 refs)

- 79-5563 Prolonged Induction of Hepatic Ornithine Decarboxylase and Its Relation to Cyclic Adenosine 3':5'-Monophosphate-dependent Protein Kinase Activation after a Single Administration of Diethylnitrosamine. (Eng) Olson, J. W. (Dept. Pharmacology, Coll. Medicine, Univ. Arizona Health Sciences Center, Tucson, AZ 85724); Russell, D. H. *Cancer Res* 39(8): 3074-3079; 1979.

The effects of a single carcinogenic dose of diethylnitrosamine (DEN: 200 mg/kg ip) on the time and extent of ornithine decarboxylase (ODC) induction and cyclic AMP (cAMP)-dependent protein kinase (PK) activation were investigated in male Sprague-Dawley rats. After a single injection of DEN, there was a rapid increase in the activity ratio of hepatic cAMP-dependent PK activity (within 1 hr) followed by the induction of ODC activity, which was detectable by 3 hr. Both the cAMP-dependent PK activity ratio and ODC activity were significantly elevated above control levels for 7 days following DEN administration. A single non-carcinogenic dose of DEN (25 mg/kg) did not increase the cAMP-dependent PK activity ratio or induce ODC activity at 24 hr postadministration. However, serial administration of DEN (25 mg/kg) for 4 or 7 days resulted in an increased cAMP-dependent PK activity ratio and increased ODC activity. This is the first report of a prolonged increase in both the activity ratio of hepatic cAMP-dependent PK and the activity of ODC in response to a single carcinogenic dose of DEN. (50 refs)

- 79-5564 Carcinogenicity of N-Nitrosobis(2-hydroxypropyl)amine and N-Nitrosobis(2-oxopropyl)amine in MRC Rats. (Eng) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42d St. and Dewey Ave., Omaha, NE 68105); Salmasi, S.; Runge, R.; Gingell, R.; Wallcave, L.; Nagel, D.; Stepan, K. *J Natl Cancer Inst* 63(1): 181-190; 1979.

To further elucidate the relationship between the molecular structures of carcinogens and their target tissues in various species and strains, the effects of N-nitrosobis(2-hydroxypropyl)amine (BHP) and N-nitrosobis(2-oxopropyl)amine (BOP) were tested in Wistar-derived MRC rats. Weekly sc injections of equitoxic doses of BHP and BOP (1/10, 1/20, or 1/40 of the LD₅₀) to the rats induced tumors at various sites. The incidence, latency, multiplicity, morphologic type, and distribution of these tumors varied according to the compound given. The esophagus was the main target organ for BHP (100%), followed by the respiratory tract (87%), pharynx (80%), colon and liver (each 73%), kidneys (20%), thyroid gland (20%), and urinary bladder and urethra (each 7%). BOP was ineffective in the esophagus and pharynx, but it induced a higher incidence of tumors in the kidneys (27%), thyroid gland (60%), urinary bladder (33%), and urethra (73%) and fewer neoplasms in the respiratory tract (20%), colon (67%), and liver (53%). In addition, BOP caused a few, apparently primary, prostate squamous cell carcinomas. When results were compared with those of BHP treatment in Sprague-Dawley rats and BHP and BOP treatment in Syrian golden hamsters, there were remarkable species and/or stock differences in the carcinogenic response. The reasons for these differences remain speculative. (34 refs)

- 79-5565 DNA Repair Synthesis in Mice Spermatids after Treatment with N-Methyl-N-nitroso-urea and N-N-Dimethylnitrosamine: Preliminary Results. (Eng) Cesarone, C. F. (Inst. Oncology, Sch. Medicine, Univ. Genoa, V.le Benedetto XV, 10 Pad. B., 16132 Genoa, Italy); Bolognesi, C.; Santi, L. *Toxicology* 12(2): 183-186; 1979.

Two methylating agents, N-methyl-N-nitrosourea (MNU: 50 or 75 mg/kg, ip) and N,N-dimethylnitrosamine (DMN: 2 or 4 mg/kg, ip), were used to evaluate a new short-term test of DNA repair synthesis based on the unscheduled incorporation of tritiated thymidine (TdR) into spermatogenic cells of male C3H mice. In the germ cells obtained from animals treated with MNU, an unscheduled DNA synthesis could be detected on the 10th day after treatment. On the 12th day, a direct dose-response relationship could be observed, and the effect persisted until the 18th day. In the animals treated with DMN, a variation in TdR incorporation was detected on day 16 after injection of the drug. The repair synthesis induced in mouse germ cells could be conveniently detected by liquid scintillation counting. (18 refs)

- 79-5566 Selected Morphological Immunocytochemical and Growth Characteristics of Three Experimental Rat Gliomas and of Their Cells In Vitro. (Eng) Stavrou, D. (Lehrstuhl für Allgemeine Pathologie und Neuropathologie, Institut für Tierpathologie der Universität München, Veterinarstrasse 13, D-8000 Munich 22, W. Germany); Osterkamp, U.; Schroder, B.; Anzil, A. P.; Zanker, K. *Exp Cell Biol* 47(1): 3-21; 1979.

Morphological and immunocytochemical studies were made of experimental brain tumors chemically induced in rats and of the cell lines established from them. Nervous system tumors were induced in Sprague-Dawley and Long-Evans rats by weekly administrations of 6 mg/kg N-methyl-N-nitrosourea in the drinking water. Three of these tumors, a grade 2 mixed glioma, a grade 2-3 astrocytoma, and a grade 1-2 oligodendroglioma, were established in culture and propagated in vitro. The mixed glioma line (75SD-G-376) and the astrocytoma line (75SD-G-420) were repeatedly subcultured, cloned at passages 90 and 120, and designated as clones 75SD-G-376C and 75SD-G-420C, respectively. The growth rate of the oligodendroglioma cell strain (77LE-G-180) was very low, and the cells died off after the fifth in vitro passage. The glial nature of all the lines was ascertained by demonstrating the presence of S-100 protein in the culture cells. Approx 2.5 yr after the 75SD-G-376 and 75SD-G-420 primary cultures were established, mass cultures as well as clones derived from them were still producing S-100 and, thus, were clearly comparable to the primary cultures, at least in this respect. However, light microscope studies showed that cells of the clonal lines, which had processes that grew shorter and became less abundant with increasing passage level, differed morphologically from cells of the primary cultures and their uncloned lines. Therefore, the cell morphology of these clones can be viewed as a form of adaptation to in vitro conditions. It is concluded that permanent cell lines with well-defined properties can be grown from experimental brain gliomas successfully established in culture and maintained in vitro. (32 refs)

- 79-5567 The Stability of Methylated Purines and of Methylphosphotriesters in the DNA of V79 Cells after Treatment with N-Methyl-N-Nitrosourea. (Eng) Warren, W. (Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Crathorn, A.R.; Shooter, K.V. *Biochim Biophys Acta* 563(1): 82-88; 1979.

V79-379A cells growing in suspension culture were treated with N-methyl-N-nitrosourea at concentrations of 0.6 and 1.2 mM. After incubation for periods from 1 to 48 hr, DNA was isolated from the cells and the concentrations of 7-methylguanine, O⁶-methylguanine, 3-methyladenine, and methyl phosphotriesters were determined. After correction for dilution resulting from DNA synthesis during the incubation, it was found that no loss of O⁶-methylguanine or methyl phosphotriesters occurred; 7-methylguanine disappeared with a half-life of 22 hr, and 3-methyladenine was detectable only immediately after the initial treatment. The results show that these cells eliminate 7-methylguanine and 3-methyladenine from DNA by a repair process but are unable to excise or repair O⁶-methylguanine or methyl phosphotriesters. (28 refs)

79-5568 Influence of Hydrogen Bonding in DNA and Polynucleotides on Reaction of Nitrogens and Oxygens Toward Ethylnitrosourea. (Eng) Bodell, W. J. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143); Singer, B. *Biochemistry* 18(13): 2860-2863; 1979.

An attempt was made to determine whether the reactivity of base-paired nitrogens and oxygens is influenced by the transient opening of the DNA helix as a function of temperature. The reactivity of ethylnitrosourea toward hydrogen-bonded sites in double-stranded DNA or poly(rA)-poly(rU) was compared with the reactivity toward those sites in single-stranded DNA, RNA, or poly(rA). Alkylation of the N-1 of adenine in poly(rA)-poly(rU) was almost suppressed at 5 C but could be markedly increased by raising the reaction temperature to 25 C, well below the T_m of 56 C. In contrast, the N-7 and N-6 of adenine, which are not hydrogen-bonded, reacted to the same extent at temperatures ranging from 5 to 65 C. The extent of reaction at the N-3 of adenine varied inversely with the reactivity of the N-1 of adenine, indicating that of these two nitrogens, N-1 is the most reactive. The proportion of reaction at the various nitrogens in poly(rA) was not affected by temperature. The hydrogen-bonded oxygens in double-stranded DNA are the O-6 of guanine, the O-4 of thymine, and the O-2 of cytosine. All are equally reactive at 5, 25, and 51 C. It is concluded that the observed temperature independence is due to these oxygens having an electron pair not involved in hydrogen bonding and, thus, available for reaction. In contrast, the electron pair of the N-1 of adenine (or the N-3 of cytosine) is involved in hydrogen bonding, and the extent of their reactivity is dependent on thermal fluctuation providing transiently open base pairs at temperatures far below the T_m. (22 refs)

79-5569 Transmission Electron Microscopy of Fetal Rat Brain Cells During Neoplastic Transformation in Cell Culture. (Eng) Haugen, A. (Human Tissue Studies Section, Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20205); Laerum, O. D. *J Natl Cancer Inst* 63(2): 455-464; 1979.

Fetal rat brain cells were investigated by transmission electron microscopy during neoplastic transformation in long-term cell cultures to determine if the cells gradually acquire surface alterations characteristic of malignant cells. Before transfer of the cells to culture, BD-IX rat fetuses were treated with a single transplacental pulse of N-ethyl-N-nitrosourea (75 µg/g) on gestation day 18. During the early stages (3-4 mo), both gliallike and neuronlike cells were present in the culture, and after 2 mo they formed complex aggregates (nodules). In contrast, corresponding

secondary control cultures consisted of flat, epithelioid neural cells without neuron or astrocyte differentiation. After 3 mo, cells with a neuron morphology gradually disappeared. Some of the remaining cells contained many autophagosomes. After 5 mo, the rapid proliferation of rather homogeneous, gliallike populations was accompanied by a reduction in the number of microfilament bundles, microtubules, and atypical nuclei. The ability of the cells to form tumors upon sc implantation into syngeneic hosts was not observed until about 3 mo later. (27 refs)

79-5570 Effect of n-Ethylnitrosourea on Rat Embryos. (Rus) Aleksandrov, V. A. (Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR). *Vopr Onkol* 25(6): 60-65; 1979.

The embryotoxicity and transplacental carcinogenicity of N-ethylnitrosourea (ENU) was studied in random-bred rats. Pregnant rats received a single iv injection of 20, 30, or 80 mg/kg ENU between days 1 and 22 of pregnancy. Administration of 20 mg/kg ENU on days 1 and 3-9 resulted in significant embryonal lethality. The teratogenic effect of ENU was most pronounced after administration on days 9 and 10. A significant increase in the incidence of tumors in the offspring was recorded after administration of ENU on day 11 (48.3% vs 9.7% in the offspring of rats inoculated with 20 mg/kg on days 8, 9, or 10). The incidence of tumors showed a progressive increase from 60.4% after inoculation on day 12 to 95.2% after inoculation on day 22. Most of the ENU-induced tumors were located in the CNS; more than one-half of neurogenic tumors were located in the brain. (8 refs)

79-5571 Carcinogenicity of Chlorinated Nitrosotrialkylureas in Rats. (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Taylor, H. W. *J Cancer Res Clin Oncol* 94(2): 131-137; 1979.

Four chlorinated nitrosotrialkylureas, which have been introduced for the treatment of cancer, were tested for carcinogenicity following po administration to Sprague-Dawley rats. The chemicals were mixed in oil at concentrations of 1.1-21.5 mg/ml, and 0.2 ml of this soln was given twice weekly for 1-50 wk. Among 45 males given nitrosochloroethylidimethylurea, 10 developed papillomas of the forestomach, 2 developed carcinomas of the forestomach, 2 developed papillomas of the esophagus, and 11 developed alveolar cell adenomas in the lung; there were 23 tumors at other sites. Among 15 males given nitrosochloroethylidimethylurea, 2 developed papillomas of the forestomach, 1 developed an alveolar adenoma, and 2 developed squamous cell carcinomas of the lung; there were 7 tumors at other sites. Of 30 females given nitrosomethylbis(chloroethyl) urea, 3 developed papillomas of the forestomach, 3 developed carcinomas of the forestomach, 1 developed a papilloma of the esophagus, and 1 developed a squamous cell carcinoma of the lung; there were 11 tumors at other sites. Of 30 females given nitrosotris(chloroethyl)urea, 9 developed papillomas of the forestomach and 2 developed alveolar cell adenomas; there were 13 tumors at other sites. (4 refs)

79-5572 Induction of Hepatic Tumors in Rats by Senkirkine and Symphytine. (Eng) Hirono, I. (Dept. Carcinogenesis and Cancer Susceptibility, Inst. Medical Science, Univ. Tokyo, Shirokanedai 4-6-1, Minato-ku, Tokyo 108, Japan);

Haga, M.; Fujii, M.; Matsuura, S.; Matsubara, N.; Nakayama, M.; Furuya, T.; Hikichi, M.; Takanashi, H.; Uchida, E.; Hosaka, S.; Ueno, I. *J Natl Cancer Inst* 63(2): 469-472; 1979.

The carcinogenicity of the pyrrolizidine alkaloids senkirkine and symphytine, which are found in coltsfoot and comfrey plants, was studied in male inbred ACI rats. Animals were divided into three groups: Groups 1 and 2 received ip injections of freshly prepared senkirkine and symphytine, respectively, at a dose of 10% of the LD₅₀ 2x/wk for 4 wk and then 1x/wk for 52 wk. Group 3 (control) was given ip injections of a 0.9% NaCl soln by the same injection schedule. All Group 1 rats survived for >290 days after the start of the injections, and 9/20 rats developed liver cell adenomas. All Group 2 animals survived for >330 days after the start of injections. Of 20 rats, 4 had liver tumors, 3 had hemangioendothelial sarcomas, and 1 had a liver cell adenoma. The hemangioendothelial sarcomas metastasized to the lungs of two rats. The control group had no liver tumors. (13 refs)

79-5573 Sister-Chromatid Exchanges and Chromosomal Breakage in Patients Treated with Cytostatics. (Eng) Musilova, J. (3rd Medical Dept., Charles Univ., Prague, Czechoslovakia); Michalova, K.; Urban, J. *Mutat Res* 67(3): 289-294; 1979.

The frequency of structural chromosome rearrangements and sister-chromatid exchanges (SCE's) in six patients being treated with cytostatic drugs was investigated in short-term phytohemagglutinin-stimulated lymphocyte cultures by means of bromodeoxyuridine substitution and the fluorescence plus Giemsa (FPG) staining technique. Both parameters were significantly increased in patients treated with comparatively low doses of cyclophosphamide, busulfan, and adriamycin. The increased SCE rate was proportional to the number of chromosome breaks, with the ratio of SCE's to breaks being about 100:1. The SCE number remained high for several months after the termination of cytostatic therapy, when the conventional analysis of chromosome breaks yielded normal results. Normal SCE values were obtained in two patients treated with low doses of fluorouracil. (11 refs)

79-5574 The Mutagenic Activity of Anti-Cancer Drugs and the Urine of Rats Given These Drugs. (Eng) Pak, K. (Dept. Urology, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto, Japan); Iwasaki, T.; Miyakawa, M.; Yoshida, O. *Urol Res* 7(2): 119-124; 1979.

The ability of 21 anticancer drugs to induce mutations in *Salmonella typhimurium* tester strains was determined in the Salmonella/microsome mutagenicity assay. Nine of the 21 anticancer drugs were mutagenic: cyclophosphamide, nitroimin, thio-TEPA, busulfan, 6-mercaptopurine, neocarzinostatin, daunomycin, adriamycin, and estramustine phosphate. Seven of these mutagens were injected continuously into the jugular veins of female Wistar rats. Urine was collected through a cystostomy tube and tested for mutagenicity. The urine from rats treated with 6/7 drugs (cyclophosphamide, nitroimin, thio-TEPA, neocarzinostatin, adriamycin, and daunomycin) was mutagenic. (23 refs)

79-5575 An Evaluation of the Use of Peripheral Blood Lymphocyte Systems for Assessing Cytological Effects In-

duced In Vivo by Chemical Mutagens. (Eng) Natarajan, A. T. (Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Lab., Univ. Leiden, Post Bus 722, Leiden, Netherlands); van Buul, P. P.; Raposa, T. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 268-274; 1978.

The use of peripheral blood lymphocyte systems for monitoring populations exposed to chemical mutagens and for screening chemicals for their in vivo mutagenic effects was investigated. Investigations included analyses of the frequency of chromosome aberrations in workers exposed to low levels of vinyl chloride; the frequencies of sister chromatid exchanges (SCE's) in blood lymphocytes from patients receiving cytostatic treatment, both during treatment and a few weeks after recovery; and chromosome aberrations and SCE's in lymphocytes of rats after in vivo treatment with directly and indirectly acting alkylating agents. No strongly significant difference was noted between the control and vinyl chloride groups of workers with regard to the occurrence and frequency of chromosome aberrations. Of the six patients treated with cytostatic drugs, five received cyclophosphamide and one thiopeta. The control group had an av of 10.3 SCE's/cell, while in the treated group two patients had significantly higher frequencies of SCE's. In a 76-yr-old patient with reticular cell sarcoma, the SCE frequencies were 23.4, 15.6, 16.2, and 12.3 per cell on days 13, 16, 18, and 20 of therapy, while the frequency decreased to 6.3 25 days after therapy was terminated. In rats, despite a very high dose of diethylnitrosamine (DEN), no effect on SCE's and chromosomal aberrations could be observed. With both dimethylnitrosamine and methyl nitrosourea, a dose-dependent increase in chromosome aberrations and SCE's was found. It is concluded that for low chronic exposures, this system is not sensitive in detecting mutagenic effects, while for assessing the in vivo effects of chemical mutagens, particularly those that need metabolic activation, this system may have value. (10 refs)

79-5576 Isolation of a Recombination Deficient *Agrobacterium tumefaciens* Mutant. (Eng) Klapwijk, P. M. (Dept. Biochemistry, State Univ. Leiden, P.O. Box 9505, 2300 RA Leiden, Netherlands); van Beelen, P.; Schilperoort, R. A. *Mol Gen Genet* 173(2): 171-175; 1979.

The isolation of a recombination deficient (Rec⁻) strain of *Agrobacterium tumefaciens* is described. Strain LBA 4011 was mutagenized with nitrosoguanidine, and after segregation 18,000 colonies were replica plated and UV irradiated. Twenty-two UV-sensitive strains were isolated and tested for methylmethanesulfonate (MMS) sensitivity. Six of these strains were more MMS-sensitive than LBA 4011. A Ti plasmid that was genetically marked with Tn 1 [Cb(R)] was introduced in these strains, and the rescue of the Cb(R) marker during superinfection with an incompatible cointegrate plasmid Ti::R 702 was determined. One strain exhibited a large reduction in rescue frequency. It is concluded that the latter strain was recombination deficient. This property did not influence the induction of plant tumors. (21 refs)

79-5577 Differential DNA Damage Induced by Chemical Mutagens in Cells Growing in a Modified Selye's Granuloma Pouch. (Eng) Lee, I. P. (Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC); Zbinden, G. *Exp Cell Biol* 47(2): 92-106; 1979.

Interactions of carcinogens with the DNA of rapidly growing granulation tissue were studied in a modified Selye's granuloma pouch in male albino rats (strain ZUR:SIV-Z). Rapid growth of granulation tissue was induced in the rats by the injection of 0.25% croton oil into an sc air pocket. The growth characteristics of the granulation tissue were evaluated by histopathologic techniques and by measuring ^3H -thymidine incorporation into DNA. The DNA of the granuloma cells was labeled with ^3H -thymidine. Subsequently, four classes of test chemicals (monofunctional and polyfunctional alkylating agents, DNA intercalating agents, and chemicals not known to interact with DNA) were injected ip. The presence of single-stranded breaks was assayed in granuloma cell DNA by the alkaline elution technique. DNA breaks were primarily induced by monofunctional alkylating agents (procarbazine, methylmethane sulfonate, cyclophosphamide, and N-methyl-N'-nitro-N-nitrosoguanidine), and they were characteristic for each compound. DNA from animals treated with polyfunctional alkylating agents (triethylenemelamine, mitomycin C, and busulfan) and DNA-intercalating agents (adriamycin, proflavin, and acriflavin) showed a variable degree of resistance to methylmethane sulfonate-induced DNA breakage. Resistance was greater with the former agents. (38 refs)

- 79-5578 Studies on the Distribution and Metabolism of N -[^{14}C]Nitrosopyrrolidine in Mice. (Eng) Johansson-Brittebo, E. (Dept. Toxicology, Univ. Uppsala, Uppsala, Sweden); Tjalve, H. *Chem Biol Interact* 25(2/3): 243-253; 1979.

Pretreatments (ip) with pyrazole (200 mg/kg), ethanol (3.1 g/kg), hialamide (500 mg/kg), or diethyldithiocarbamate (350 mg/kg) strongly depressed the exhalation of $^{14}\text{CO}_2$ and the incorporation of radioactivity in the acid-insoluble fraction of the liver in mice injected with N -[^{14}C]nitrosopyrrolidine (^{14}C -NP, 2.0 μCi ; 0.6 mg/kg). Whole-body autoradiography performed with hemisections of pretreated and non-pretreated mice at -80 C (to prevent evaporation of the volatile NP) and with dry tape-sections (to localize the nonvolatile metabolites) indicated a uniform distribution of the nonmetabolized NP in the tissues. At the shortest survival intervals (1 and 5 min), a high level of metabolites was found in the liver, the tracheobronchial and nasal mucosa and Harder's gland, indicating a local formation of metabolites in these tissues. At later survival intervals (0.5-24 hr) metabolites were also found in tissues with a rapid cell turnover and a high rate of protein synthesis and in brown fat; this may reflect incorporation of metabolites via normal biosynthetic pathways. Autoradiography of ^{14}C -NP administered po in mice resulted in distribution pictures similar to those obtained after iv injections. (27 refs)

- 79-5579 Adaptive Response to Alkylating Agents Involves Alteration In Situ of O 6 -Methylguanine Residues in DNA. (Eng) Karran, P. (Dept. Medical Chemistry, Univ. Gothenburg, 40033 Gothenburg, Sweden); Lindahl, T.; Griffin, B. *Nature* 280(5717): 76-77; 1979.

The nature of the error-free repair system that removes O 6 -methylguanine (OMG) residues from *Escherichia coli* DNA alkylated by N-methyl-N-nitrosourea (MNU) was investigated in vitro using [Me- ^3H]MNU-treated *Micrococcus luteus* DNA and cell-free extracts (CFE's) from nonadapted and adapted *E. coli*. The extracts were adapted by growth for 90 min in the presence of 1 $\mu\text{g}/\text{ml}$ N-methyl-N'-nitro-N-nitrosoguanidine, and they possess increased resistance to alkylating agents. The MNU-treated DNA was preincubated for 16 hr at 80 C in neutral soln to release

purines methylated at the 7 and 3 positions and yet retain the double-stranded DNA structure. When DNA containingq OMG was incubated with nonadapted and CFE's, precipitated with cold ethanol or trichloroacetic acid, and subjected to mild acid hydrolysis to release free purines, paper chromatography of the hydrolysate demonstrated that with increasing amounts of adapted CFE in the reaction mixtures, decreasing amounts of OMG were recovered. Moreover, no OMG was released in an ethanol- or acid-soluble form at the end of the incubation period, and only after the hydrolysis step was the radioactivity in the OMG residues converted to a volatile product (presumably methanol), indicating that the repair system in adaptation either transfers the O 6 -methyl group to another site or that OMG residues are destroyed in situ (eg, by ring cleavage). When the radioactive material in reaction mixtures treated with an adapted CFE (90% disappearance of OMG from DNA) was treated with Pronase (2 mg/ml) or pancreatic RNase (100 $\mu\text{g}/\text{ml}$), no ethanol-soluble radioactivity was released. When this material was treated with pancreatic DNase I (100 $\mu\text{g}/\text{ml}$), however, 80% of the radioactivity was converted to ethanol-soluble form. Similar results were obtained in control experiments with DNA incubated with nonadapted CFE. Thus, the radioactive methyl groups in the ethanol-precipitable material generated from OMG residues by treatment with the adapted CFE remain in DNA and are not transferred to a protein or RNA molecule. Mutants defective in the adaptive response were isolated, and the inducible enzyme responsible for adaptation appears to be the product of a single gene. (11 refs)

- 79-5580 Thioether Concentration and Mutagenicity of Urine from Cigarette Smokers. (Eng) van Doorn, R. (Inst. Pharmacology and Toxicology, Univ. Nijmegen, Nijmegen, Netherlands); Bos, R. P.; Leijdekkers, C. M.; Wagenaar-Zegers, M. A.; Theuvs, J. L.; Henderson, P. T. *Int Arch Occup Environ Health* 43(3): 159-166; 1979.

The mutagenicity of thioethers for *Salmonella typhimurium* strain TA1538 and the urinary excretion of these compounds by smokers and nonsmokers were studied. The urinary concentrations of thioethers increased significantly in smokers compared with nonsmokers, and they increased with the number of cigarettes smoked per day. Compared with nonsmokers, persons smoking up to 10 cigarettes/day showed no increase in the excretion of urinary mutagens, but the excretion of mutagens was significantly increased in persons smoking >10 cigarettes/day. The increase in urinary mutagens was not reflected by a concomitant increase in urinary thioethers. Urinary thioether and mutagen excretion was monitored in a single subject who increased the number of cigarettes smoked/day from 0 to 20 over a 20-day period. The appearance in the urine of mutagens inhaled during smoking and excreted unchanged or as metabolites correlated fairly well with the number of cigarettes smoked that day. However, excretion of thioethers responded more slowly to changes in the number of cigarettes smoked. The data indicate that cigarette smoking may interfere with the results of tests used to monitor occupational exposure to potential alkylating agents. (20 refs)

- 79-5581 Mutagenic Activities of Hydroperoxythymine Derivatives, Products of Radiation and Oxidation Reactions. (Eng) Wang, S. Y. (Dept. Environmental Health Sciences, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD 21205); Hahn, B. S.; Batzinger, R. P.; Bueding, E. *Biochem Biophys Res Commun* 89(1): 259-263; 1979.

To determine whether the chemical reactivities of the pyrimidine hydroperoxides are correlated with their mutagenicities, the efficacies of *cis*-5,6-dihydro-6-hydroperoxy-5-hydroxythymine (6-TOOH) and 5-hydroperoxymethyluracil (α -TOOH) in the inactivation of *Hemophilus influenzae* transforming DNA were compared. α -TOOH, which is about 10^3 -fold less chemically reactive than 6-TOOH, was approx 10^3 -fold more effective in the biological inactivation. *Salmonella typhimurium* strains TA100 and TA98 were used to determine whether mutations could result from different steric interactions with DNA molecules. In this system, various hydroperoxy derivatives of thymine and thymidine produced by ionizing radiation, near-UV radiation, and certain oxidation reactions were highly mutagenic. In general, the hydroperoxy derivatives required no metabolic activation. If these data reflect the general toxicity of these compounds for humans, radiation products and certain oxidation products should be considered potential human health hazards. (15 refs)

79-5582 Effects of the Comutagens, Harman and Norharman, on the Interaction of a Tryptophan Pyrolysis Product, 3-Amino-1-methyl-5H-pyrido(4,3-b)indole with DNA. (Eng) Lau, P. P. (Dept. Chemistry, Massachusetts Inst. Technology, Cambridge, MA 02139); Luh, Y. *Biochem Biophys Res Commun* 89(1): 188-194; 1979.

Harman and norharman, both of which are comutagens of many chemicals, were tested for their effect on the binding of DNA to 3-amino-1-methyl-5H-pyrido(4,3-b)indole (Trp-P-2), a potent mutagen found with harman and norharman in the pyrolysate of tryptophan. Neither comutagen significantly affected the binding of Trp-P-2 to DNA in the absence of microsomal proteins, although a slight decrease in affinity occurred at extremely high concentrations (1 mM) of harman. A covalent binding study revealed that both comutagens inhibited rather than enhanced the binding of Trp-P-2 to DNA in the presence of 3-methylcholanthrene-induced male Fischer rat liver microsomes. The mutagenesis of Trp-P-2 has also been shown to be inhibited by harman and norharman. Thus, the inhibiting action of these compounds is largely enzymatic in contrast to noncovalent binding. It is suggested that the so-called "enhancing" effect of the comutagens on mutagenesis under an unfavorable enzymatic condition might be an artifact of the assay method. (16 refs)

79-5583 A Collaborative Dominant Lethal Study of Triethylenemelamine in the Rat. (Eng) Moreland, F. M. (Div. Toxicology, Food and Drug Admin., Washington, DC 20204); Kilian, D. J.; Palmer, K. A.; Springer, J. A.; Green, S.; Legator, M. S. *Toxicol Appl Pharmacol* 49(1): 161-170; 1979.

A collaborative dominant lethal study of the known mutagen triethylenemelamine (TEM) was conducted in male rats. Six laboratories were supplied with animals from a common source and with TEM of the same lot number in an attempt to guarantee uniformity of strain and drug effect. Male Sprague-Dawley rats which were proven breeders were divided into five groups of 15 animals each and were given a single ip injection of TEM at 0 (saline), 0.125, 0.250, 0.375, or 0.500 mg/kg, respectively. After the injection, each male was housed with two virgin females (200 g) each week for a 10-week period. The females were sacrificed by asphyxiation 14 days after the midweek of cohousing, and corpora lutea were counted and the uterine contents examined. The results showed a highly significant difference among laboratories for the number of corpora lutea per pregnant female and for preimplanta-

tion losses over all doses and weeks. Variability among laboratories was least for total implants in both treated and control groups and dead implants in the control group. Although the variation was great between laboratories with respect to the several parameters considered, the results obtained by each laboratory did show that TEM has a significant mutagenic effect in the dominant lethal test. (13 refs)

79-5584 In Vivo Alkylation of Foetal, Maternal and Normal Rat Tissue Nucleic Acids by 3-Methyl-1-phenyltriazen. (Eng) Margison, G. P. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Likhachev, A. J.; Kolar, G. F. *Chem Biol Interact* 25(2/3): 345-353; 1979.

The carcinogen 3-methyl-1-phenyltriazen (MPT: 80 mg/kg) was administered sc to normal or pregnant BD VI rats, and DNA and RNA were isolated from various tissues after 8 or 15 hr, respectively. Sephadex G-10 chromatography of DNA hydrolysates showed the presence of 7-methylguanine in all tissues examined, including that of the brain, one of the target organs for tumor induction. The amounts of the minor product O⁶-methylguanine were characteristic of an SN₁ reaction mechanism. Dowex-50 chromatography of RNA hydrolysates showed the presence of 7-methylguanine and of another minor product, 3-methylcytosine. The relative amounts, both of methylated bases in the individual nucleic acids and of 7-methylguanine in DNA and RNA were similar to those found previously after administration of 3,3-dimethyl-1-phenyltriazen (DMPT). This suggests the involvement of a common alkylating intermediate. De novo incorporation of radioactivity into purine bases was detected in both DNA and RNA, although the levels were not related to the amounts of methylation. The results show that MPT is sufficiently stable to alkylate nucleic acids in vivo, and they are consistent with the hypothesis that this reaction is a prerequisite for tumor induction. Furthermore, they support the proposal that MPT is the active intermediate in the induction of tumors by DMPT. (22 refs)

79-5585 Inhibition of DNA Synthesis by Nitroheterocycles. I. Correlation with Half-Wave Reduction Potential. (Eng) Olive, P. L. (Radiobiology Section, Johns Hopkins Oncology Center, 601 North Broadway, Baltimore, MD 21117). *Br J Cancer* 40(1): 89-93; 1979.

Twenty-one nitroheterocycles, including metronidazole, misonidazole, and AF-2, were tested for their ability to inhibit DNA synthesis in mouse L-929 cells growing in culture. All tested drugs inhibited the rate of ³H-thymidine incorporation into L cells following drug treatment for 4 hr under aerobic conditions. Only four drugs reached their limits of solubility before ³H-thymidine uptake was inhibited by 50% or more. For the remaining 17, the log of the concentration producing 50% inhibition of incorporation was directly correlated with the half-wave reduction potential of the compound. (17 refs)

79-5586 Absence of Genotoxic Effects of Metronidazole and Two of Its Urinary Metabolites on Human Lymphocytes In Vitro. (Eng) Lambert, B. (Dept. Clinical Genetics, Karolinska Hosp., 104 01 Stockholm, Sweden); Lindblad, A.; Ringborg, U. *Mutat Res* 67(3): 281-287; 1979.

The genotoxicity of the antiprotozoan agent metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] and two of its major human urinary excretion products, 2-methyl-5-nitroimidazole-1-yl acetic acid and 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole, was tested in human lymphocytes in vitro by analysis of chromosome aberrations, sister-chromatid exchanges and DNA-repair synthesis. The positive control compounds methyl methanesulfonate (MMS) and nitrogen mustard (NH_2) showed significant genotoxic activity in these tests. No such activity of metronidazole and its two metabolites was detected in concentrations up to 1,000 $\mu\text{g}/\text{ml}$ (5.8×10^{-3} M). These three compounds also had no influence on the DNA-repair synthesis induced by MMS and HN_2 . The results suggest that metronidazole and its urinary metabolites have no direct genotoxic effect on human lymphocytes in vitro. (26 refs)

- 79-5587 Absence of Chromosomal Damage in the Lymphocytes of Patients Treated with Metronidazole for *Trichomoniasis vaginalis*. (Eng) Hartley-Asp, B. (AB Leo, Res. Labs., Helsingborg, Sweden). *Toxicol Lett* 4(1): 15-19; 1979.

The peripheral blood lymphocytes of 12 patients (19-48 yr old) receiving metronidazole (200 mg tid for 7 days) for *Trichomoniasis vaginalis* infections were analyzed for chromosome aberrations. Samples were taken before, during, and 3 wk after completion of treatment, with each patient acting as her own control. No increase in chromosome aberration frequency was found for any aberration type, either for the individual or for the group means. Thus, short-term metronidazole treatment did not produce any clastogenic effect on human lymphocytes in vivo. (14 refs)

- 79-5588 The Action of Rat Cytosol Enzymes on Some Methylated Nucleic Acid Components Produced by the Carcinogenic N-Nitroso Compounds. (Eng) O'Connor, P. J. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester M20 9BK, England); Saffhill, R. *Chem Biol Interact* 26(1): 91-102; 1979.

The stability of several O- and N-methylated nucleic acid derivatives was examined in the presence of cytosol extracts from a variety of male Wistar rat tissues. An activity capable of demethylating O⁶-methyldeoxyguanosine was readily detectable in all tissues examined. Arranged in approx order of decreasing specific activity, these tissues are as follows: small intestine, spleen, kidney, lung, liver, skin, heart, and brain. The in vitro requirements for the activity derived from liver and the observations that O⁶-methylguanine and its deoxynucleoside 5'-monophosphate are insensitive to the action of these extracts suggest that this activity may be due to an enzyme that resembles adenosine deaminase. In contrast to the ready degradation of O⁶-methyldeoxyguanosine, the corresponding ethyl derivative was degraded much more slowly. There was no evidence of degradation of the O²- and O²-methyldeoxythymidines, even after exposure of these components to cytosol enzymes for up to 90 min. Similarly, no demethylation of 3-methyldeoxycytidine, 3-methyldeoxythymidine, 1-methyldeoxyadenosine, and 7-methyldeoxyguanosine was detected. (33 refs)

- 79-5589 Quantitation of the Adaptive Response to Alkylating Agents. (Eng) Robins, P. (Imperial Cancer Res. Fund,

Mill Hill Labs., Burtonhole Lane, London NW7, England); Cairns, J. *Nature* 280(5717): 74-76; 1979.

Experiments were carried out to investigate the nature of the fast and slow reactions in the adaptive response of *Escherichia coli* AB1157 to treatment with alkylating agents, particularly N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), that convert guanine to O⁶-methylguanine (OMG). Adapted and nonadapted bacterial cultures were used in experiments involving challenge with 10 or 50 $\mu\text{g}/\text{ml}$ 3H-MNNG for 2 min; adapted cells had been previously exposed to 0.5 $\mu\text{g}/\text{ml}$ MNNG for 90 min. When adapted bacteria were challenged with the 10- μg dose and nonadapted bacteria with the 50- μg dose (so that the OMG content of the two cultures was the same after challenge and both cultures were outgrown in the absence of MNNG, OMG was lost at equal rates from both cultures. If the challenge dose was the same, however, adapted bacteria lost OMG sooner than did nonadapted bacteria. Hence, adapted and nonadapted bacteria appear to differ only in the presence of the fast reaction; the slow reaction seems to be some constitutive form of repair that cannot be enhanced by adaptation. When adapted and nonadapted bacteria were challenged and then outgrown at 37 C, at 0 C, or at 37 C in the presence of 100 $\mu\text{g}/\text{ml}$ chloramphenicol, the fast reaction but not the slow reaction occurred, demonstrating that the fast reaction is carried out by gene products that have accumulated during adaptation and are used up during challenge, but the slow reaction represents the induced synthesis and immediate action of these same gene products. The fact that the molecules that remove OMG units appear to be used up in the response could explain two phenomena: (1) large doses of alkylating agents inhibit the capacity of cells to handle subsequent small doses of these agents and (2) certain nitrosamines exhibit high carcinogenicity in animals (in which doses are usually high) but low mutagenicity in the Ames test (in which doses are usually low); the first system may be saturated, whereas the second one is not. (15 refs)

- 79-5590 Inhibition of Nitroso Chemical Carcinogen Activation of Rat Hepatic Guanylate Cyclase by Anticancer Agents. (Eng) Vesely, D. L. (Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Arkansas Medical Sch., 4301 W. Markham, Little Rock, AR 72201); Levey, G. S. *Oncology* 36(3): 122-126; 1979.

The effect of three major classes of anticancer chemotherapeutic agents, antimetabolites (methotrexate and 6-mercaptopurine), antitumor antibiotics (adriamycin and actinomycin D), and alkylating agents (cytoxan, uracil mustard, isophosphamide, chlornaphazine, and 1-propanol-3,3'-iminodimethane sulfonate) on the activation of guanylate cyclase (GC) by nitroso chemical carcinogens was examined. The anticancer chemotherapeutic agents noncompetitively blocked the activation of rat hepatic GC by N'-nitro-N-nitroso-N-propylguanidine (NNPG) and hydrazine. Adriamycin, methotrexate, and uracil mustard were the most effective inhibitors, completely abolishing the effect of 1 mM NNPG on GC activity. The remainder of the agents abolished the NNPG activation of GC 40%-70%. Since a previously described GC inhibitor has been shown to terminate the growth of an undifferentiated prostatic cancer in tissue culture, the present data may indicate that one of the mechanisms by which anticancer chemotherapeutic agents exert their effects is by inhibition of tumor GC activity. (21 refs)

- 79-5591 Intestinal Metaplasia and Adenocarcinoma Induced in the Stomach of Rats by N-Propyl-N'-nitro-N-

nitrosoguanidine. (Eng) Sasajima, K. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo, Japan); Kawachi, T.; Matsukura, N.; Sano, T.; Sugimura, T. *J Cancer Res Clin Oncol* 94(2): 201-206; 1979.

The effects of long-term po administration of N-propyl-N'-nitro-N-nitrosoguanidine (PNNG), the propyl derivative of MNNG, were determined in Wistar Rats. PNNG was administered to the rats at a concentration of 59.5 µg/ml in the drinking water for 4, 8, or 12 mo, and the rats were killed in the 15th month. Intestinal metaplasia was induced in the glandular stomachs of 25%, 75%, and 83% of the rats treated for 4, 8, and 12 mo, respectively. Metaplastic glands were found in the pyloric region, especially near the pyloric ring. These glands contained goblet cells and columnar cells with striated borders. No tumors were found in the stomach of rats after 4 mo of treatment, but adenomas (3/15 rats) were found after 8 mo of treatment, and both adenomas (5/6) and adenocarcinomas (2/6) were found after 12 mo of treatment. PNNG is a weaker carcinogen than N-methyl-N'-nitro-N-nitrosoguanidine. The present system should be useful in further studies of intestinal metaplasia and of the relationship between intestinal metaplasia and gastric carcinoma. (10 refs)

79-5592 Interactions of the Carcinogen 4-Nitroquinoline 1-Oxide with the Non-protein Thiols of Mammalian Cells. (Eng) Varnes, M. E. (Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH 44106); Biaglow, J. E. *Cancer Res* 39(8): 2960-2965; 1979.

Some of the factors that influence the reaction of 4-nitroquinoline 1-oxide (4-NQO) with the nonprotein thiols (NPSH) of whole cells were investigated. 4-NQO rapidly depleted the NPSH from Ehrlich ascites tumor cells and V79 Chinese hamster fibroblasts. The effects of NPSH on 4-NQO metabolism were studied by measuring 4-hydroxyaminoquinoline 1-oxide (4-HAQO) formation, cyanide ion-insensitive oxygen consumption, and reduction of ferricytochromes $c + c_1$ in normal cells and in cells pretreated with the thiol reagent N-ethylmaleimide. Removal of thiols before treatment with 4-NQO resulted in an increased production of 4-HAQO and an increased production of nitro radicals. The NPSH thus appeared to play a significant role in 4-NQO detoxification. Glutathione, when present in culture medium during 4-NQO treatment, protected V79 cells from 4-NQO toxicity. Several mechanisms for the reaction of 4-NQO with intracellular NPSH were indicated. Both V79 and Ehrlich cells contained appreciable amounts of glutathione S-transferase, which catalyzes the nucleophilic substitution of the nitro group of 4-NQO with thiols. Greater thiol loss under oxic than under hypoxic conditions suggested oxidation by superoxide, peroxide, or hydroxyl radical formed during 4-NQO reduction. In addition, reaction of thiols with nitro radicals or with nitrosoquinoline 1-oxide was indicated by the inhibitory effect of glutathione on oxygen consumption in solns of 4-NQO and sodium ascorbate. (27 refs)

79-5593 Possible Use of Fish and Amphibia for Detecting the Carcinogenic Effect of Nitrosomorpholine and Its Chemical Precursors. (Rus) Khudolei, V. V. (Lab. Chemical Carcinogens, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Anikin, I. V.; Sirenko, O. A.; Pliss, G. B. *Vopr Onkol* 25(6): 70-75; 1979.

The carcinogenic effect of nitrosomorpholine (NM) and its chemical precursors was evaluated in frogs (*Rana temporaria*) and

aquarium fish (*Danio rerio* and *Xiphophorus helleri*) in two series of experiments. In series I, frogs were kept in water containing 6 mg/liter of NM, 40 mg/liter of sodium nitrite (SN), 20 mg/liter of morpholine, or SN + morpholine; duration of exposure ranged from 44 to 70 wk. The first NM-induced tumors were detected at 7 wk (av latent period of tumor development was 24 wk); 17/37 surviving frogs had tumors (7 had liver tumors and 10 had generalized tumors of the blood system). Frogs exposed to SN or morpholine alone were free of tumors, but 10/34 frogs exposed to SN + morpholine developed tumors (1 had a benign tubular-trabecular hepatic adenoma, 4 had hepatocellular carcinomas (HCC's), and 5 had generalized hemoblastoses). The av latent period of tumor development was 32 wk. In series II, fish were kept in water containing 0.1-0.3 mg/liter of NM, 7.3 mg/liter of SN, 3.6 mg/liter of morpholine, or SN + morpholine; duration of exposure ranged from 28 to 52 wk. Of 24 *D. rerio* fish exposed to NM, 8 developed tumors (av latent period was 16-22 wk). There were 7 HCC's, 4 adenocarcinomas of the intestine, and 1 mesenchymoma. Of 17 *X. helleri* fish exposed to NM, 5 developed HCC's (av latent period was 23 wk). Both species exposed to SN or morpholine alone were free of tumors. Exposure to SN + morpholine induced tumors in 2/9 *D. rerio* fish (2 HCC's, and 1 adenomatous polyp of the intestine; av latent period was 42 wk) and in 2/5 *X. helleri* fish (2 HCC's; av latent period was 42 wk). The use of aquatic animals as indicators of water pollution by nitrosamines and their precursors is discussed. (12 refs)

79-5594 Chemical Reactivities and Oncogenicities of a Series of N-Hydroxyheterocycles. (Eng) Lee, T. C. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Teller, M. N.; Budinger, J. M.; Klotzer, W.; Brown, G. B. *Chem Biol Interact* 25(2/3): 369-372; 1979.

Because the oncogenicity of certain N-hydroxypurines was found to be paralleled by a unique chemical reactivity of their ester derivatives, ie, the esters undergo elimination-substitution (SN1') reactions to yield 8-substituted xanthines, a series of six ring analogs of 3-hydroxyxanthine was investigated to determine the structural features required for this type of SN1' reactivity. Selected compounds from the series were also assayed for carcinogenicity. Comparisons of the reactivities of the six compounds from previous reports showed that the ability of each compound to undergo an SN1' reaction is: 1-hydroxy-2,4-dioxypyrrrolopyrimidine (I) > 3-hydroxyxanthine (II) > 3-hydroxy-2-oxopurine (III) > the N-hydroxy derivative of quinazoline (IV) > the N-hydroxy derivative of pyridopyrimidine > the N-hydroxy derivative of pteridine. This order agrees with predictions made from the relative π -electron densities of the pyrrole, imidazole, benzene, pyridine, and pyrazine ring systems, with III being placed after II because of its lack of a 6-oxo group. Since only the π -electron-excessive ring systems exhibit high reactivity, only I, II, and III were assayed for carcinogenicity along with 1-hydroxyuracil, the parent pyrimidine derivative. The compounds were administered sc 3x/wk for 8 wk to groups of 20 male CD rats that were followed for 18 mo. The failure of I to induce any tumors at a dose of 1.0 mg/injection may be due to its extreme reactivity. Compound II induced tumors in 108/115 rats at a dose of 1.0 mg/injection and in 32/77 rats at a dose of 0.1 mg/injection. Compound III was weakly oncogenic (3/20 rats had tumors), a result that may be due to its susceptibility to xanthine oxidase, which is present in sc tissues. 1-Hydroxyuracil induced tumors in 1/18 rats. It appears that the appropriate degree of reactivity in an SN1' reaction is peculiar to the purine ring. (23 refs)

79-5595 Hormone Secretion by Dispersed Cell Cultures of Human Pituitary Adenomas: Effects of Theophylline,

Thyrotropin-releasing Hormone, Somatostatin, and 2-Bromo- α -ergocryptine. (Eng) Adams, E. F. (Endocrine Unit, Dept. Medicine, Royal Postgraduate Medical Sch., Hammersmith Hosp., London, W12 OHS, England); Brajkovich, I. E.; Mashiter, K. *J Clin Endocrinol Metab* 49(1): 120-126; 1979.

A dispersed cell culture system was used to examine basal and modulated secretion of prolactin (PRL) and growth hormone (GH) by human somatotrophic (ST), lactotropic (LT), and mixed ST-LT pituitary adenomas. The 24-hr secretion of PRL by a normal pituitary and by a LT and a mixed adenoma increased with time in culture. The secretion rate from the mixed adenoma was 18-fold higher on day 20 than on day 1, with 225 μ g PRL being produced from 4×10^5 cells. PRL secretion was still elevated after 36 days of culture. GH secretion always decreased rapidly from day 1. Initial GH secretion in cultures of a ST adenoma was 18 times of that from the same number of normal pituitary cells. Theophylline (10^{-2} M) significantly stimulated GH secretion by ST and mixed adenoma cells during a 4-hr incubation after 4 and 28, but not 49, days in culture. PRL secretion was only stimulated at 28 days. Thyrotropin-releasing hormone stimulated PRL and GH secretion from adenomas in a dose-dependent manner, with 10 nanograms (ng)/ml being max. Somatostatin alone at doses up to 100 ng/ml had no consistent effect on GH secretion, but it completely blocked the twofold stimulation induced by 10^{-2} M theophylline. 2-Bromo- α -ergocryptine increasingly inhibited basal PRL and GH secretion up to the max dose used (10 μ g/ml), and it virtually abolished the theophylline-induced stimulation of GH and PRL secretion at this dose. These results show that dispersed cell cultures of human pituitary adenomas can be satisfactorily maintained for at least 28 days and that they autonomously secrete PRL but not GH during this period. The modulation of PRL and GH secretion by various agents indicates the value of this technique for the direct study of functioning human pituitary adenomas. (32 refs)

79-5596 Caffeine, Cyclic Nucleotides, and Breast Disease. (Eng) Minton, J. P. (Dept. Surgery, Ohio State Univ. Coll. Medicine, 410 W. 10th Ave., Columbus, OH 43201); Foelcking, M. K.; Webster, D. J.; Matthews, R. H. *Surgery* 86(1): 105-109; 1979.

The clinical effect of removing methylxanthine (MX) from the diets of 47 women with clinical fibrocystic disease of the breast was studied. Twenty of the patients abstained totally from MX consumption. All experienced a headache for 1-7 days after beginning abstinence. Of these 20 women, 13 experienced complete disappearance of all palpable breast nodules and other symptoms within 1-6 mo after eliminating MX from their diets, whereas only 1/27 of women who continued MX consumption experienced disease resolution ($p < 0.001$). The mean age of the 13 women who discontinued MX consumption and experienced disease resolution was 35 yr, compared with 45 yr in the group who ceased MX consumption but did not experience disease resolution. Cyclic AMP levels in the fibroadenomatous tissue increased as the deviation of the tissue from normal increased. Elevations in cyclic guanosine monophosphate were more transient. Long-term follow-up studies indicated that breast disease returned when MX consumption was resumed, but it remained resolved when abstinence from MX was continued. The possibility that MX consumption is related to the development of malignancy should be considered. (12 refs)

79-5597 A Carcinogen with a Bridged Bay Region: Synthesis, X-Ray Structure, and Biological Activity of 15,16-

Dihydro-1,11-methanocyclopenta(α)-phenanthren-17-one. (Eng) Bhatt, T. S. (Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Coombs, M. M.; Kissonerghis, A. M.; Clayton, A. F.; McPartlin, M. *J Chem Soc Chem Commun* 10: 433-434; 1979.

15,16-Dihydro-1,11-methanocyclopenta(α)phenanthren-17-one was synthesized, and its x-ray structure was determined. Although it has a bridged bay region, it is a carcinogen. (6 refs)

79-5598 Substitutional Effects of Styrene Oxides on Survival and Mutation Induction in Cultured Chinese Hamster Cells (V-79)*. (Eng) Sugiura, K. (Inst. Ecotoxicology, Gakushuin Univ., Toshima-ku, Tokyo 171, Japan); Maeda, A.; Goto, M. *Chemosphere* 8(6): 369-372; 1979.

A study of the effects of 3,4-dimethyl-, p-methyl-, m-chloro-, and unsubstituted styrene oxide on survival and on the induction of 6-thioguanine-resistant mutations revealed that mutagenicity and lethality increased in the order: styrene oxide < m-chlorostyrene oxide < p-methylstyrene oxide < 3,4-dimethylstyrene oxide. There was an inverse correlation between LD₅₀ values and retention time. (10 refs)

79-5599 Inhibition of Promutagen Activation by the Antioxidants Butylated Hydroxyanisole and Butylated Hydroxytoluene. (Eng) McKee, R. H. (Litron Labs., Ltd., Ontario Res. Inst., 1351 Mt. Hope Ave., Rochester, NY 14620); Tometsko, A. M. *J Natl Cancer Inst* 63(2): 473-477; 1979.

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) exhibited antimutagenic activity in the *Salmonella typhimurium* reversion test. Both BHA and BHT reduced the revertant yields induced by chemicals requiring metabolic activation for effectiveness. However, they did not affect reversion induced by direct-acting mutagens. These results suggest that BHA and BHT may inhibit metabolic activation processes, and they demonstrate that the *S. typhimurium* reversion test may be used to identify inhibitors of neoplasia. (33 refs)

79-5600 Effect of 2(3)-tert-Butyl-4-hydroxyanisole Administration on the Activities of Several Hepatic Microsomal and Cytoplasmic Enzymes in Mice. (Eng) Cha, Y. N. (Dept. Pathobiology, Johns Hopkins Medical Institutions, Baltimore, MD 21205); Bueding, E. *Biochem Pharmacol* 28(12): 1917-1921; 1979.

The effect of 2(3)-tert-butyl-4-hydroxyanisole (BHA) on hepatic microsomal and cytoplasmic enzyme activities was studied in CD-1 mice. When the mice were fed a powdered diet containing 0.75% BHA (wt/wt), the activities of several hepatic enzymes increased markedly. This was associated with increased liver wts and total protein contents, especially of the microsomal and cytosol fractions. Although the specific level of cytochrome P-450 was decreased slightly in the microsomes, the specific level of cytochrome b₅ and the specific activities of the cytochrome c reductases (NADPH- or NADH-dependent) were increased twofold. There was a slight decrease in the specific activities of aminopyrine demethylase and benzo(a)pyrene hydroxylase, but both aniline hydroxylase and uridine diphosphate (UDP)-glucuronyltransferase activities were increased (2.7- and 4.6-fold,

respectively). The specific activity of a microsomal membrane marker enzyme, glucose-6-phosphatase, was decreased slightly (25%). In the cytosol fraction, the specific activities of glucose-6-phosphate dehydrogenase and of UDP-glucose dehydrogenase were increased 3.8- and 6.1-fold, respectively. Differences were noted in the time courses of the increase and decrease in these enzyme activities after initiation and discontinuation of BHA treatment. (38 refs)

- 79-5601 Nasocytologic Examination of Wood Industry Workers. (Eng) Drettner, B. (Dept. Otolaryngology, Univ. Hosp., Huddinge, Sweden); Stenkvist, B. *Acta Otolaryngol [Suppl] (Stockh)* 360: 122-123; 1979.

Two methods for the field examination of furniture industry workers (nasal rinsing and direct sample-taking from the middle meatus) were evaluated for their applicability to the early diagnosis of ethmoidal cancer. Among 715 Swedish wood workers, direct sampling proved superior to the rinsing method in that samples obtained by the former method contained up to 88% cylinder cells as compared with only 2% obtained by the latter method. No cancerous or precancerous changes could be identified in any of the workers examined. (6 refs)

- 79-5602 The Interaction of Styrene Oxide with Hepatic Cytochrome P-450 In Vitro and Effects of Styrene Oxide Inhalation on Xenobiotic Biotransformation in Mouse Liver and Kidney. (Eng) Vainio, H. (Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland); Elovaara, E. *Biochem Pharmacol* 28(13): 2001-2004; 1979.

During the 5-day recovery period after acute inhalation intoxication with styrene oxide (SO: 6 hr/day, 3 days at 200, or 100 ppm), a transient rise in mouse liver and kidney microsomal 7-ethoxycoumarin O-deethylase activity paralleled changes in cytochrome P-450 levels. Microsomal epoxide hydratase and Uridine diphosphate-glucuronosyltransferase activities were unaffected. In the presence of hepatic microsomes from phenobarbital (PB)-treated mice, SO produced a characteristic Type I difference spectrum. SO binding is catalyzed by more than one type of P-450 hemoprotein, but predominantly by PB-induced cytochrome P-450. In PB-pretreated microsomes, SO had two spectral dissociation constants, 0.05 and 0.4 mM. (18 refs)

- 79-5603 Cytogenetic Activity of Some Common Antioxidants and Their Interaction with X-Rays. (Eng) Kaul, B. L. (Regional Res. lab., Jammu, Tawi, 180001, India). *Mutat Res* 67(3): 239-247; 1979.

The cytogenetic activity of butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, and p-methoxyphenol, phenolic antioxidants widely used to preserve and stabilize foods rich in fats and oils, was investigated in barley seeds and onion root tips. The treatments reduced seed germination and induced a significant amount of seedling injury. Only the p-methoxyphenol treatments produced a moderate amount of chromosome aberrations. Being strong antioxidants, it was expected that pretreatment of the two plant systems with these compounds would reduce the cytogenetic damage caused by x-radiation. Contrary to expectation, however, radiation damage, measured as seed and seedling lethality and

chromosome aberrations, was increased significantly. Postirradiation treatment with the antioxidants also increased the radiation damage. The damage was, however, reduced by postirradiation treatment with ATP. (16 refs)

- 79-5604 Elevation of Extrahepatic Glutathione S-Transferase and Epoxide Hydratase Activities by 2(3)-tert-Butyl-4-hydroxyanisole. (Eng) Benson, A. M. (Dept. Pharmacology and Experimental Therapeutics; Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205); Cha, Y. M.; Bueding, E.; Heine, H. S.; Talalay, P. *Cancer Res* 39(8): 2971-2977; 1979.

A study was made of the effects of 2(3)-tert-butyl-4-hydroxyanisole (BHA: 7.5 g/kg diet) on glutathione S-transferase (GST) and microsomal epoxide hydratase (EH) levels and on the concentrations of nonprotein thiol compounds in extrahepatic tissues of female CD-1 mice and male Sprague-Dawley rats. BHA resulted in elevated GST and EH activities in multiple extrahepatic tissues of the mice and rats. In mice, GST specific activities in cytosol doubled in the lung and stomach and increased to 15 times control levels (with 1,2-dichloro-4-nitrobenzene as substrate) in the small intestine. Microsomal EH specific activity toward styrene oxide doubled in the mouse colon and stomach and increased to nearly six times control levels in the small intestine. These enzymes were enhanced in several other mouse tissues and in rat small intestine, kidney, and lung. In mice, BHA increased the concentrations of nonprotein sulfhydryl compounds in the mucosa of several digestive tract tissues as well as in the urinary bladder. EH is a detoxifying enzyme that inactivates numerous mutagenic epoxides. However, elevation of EH activity may not necessarily exert a protective function in the case of all arene oxides, since at least some forms of this enzyme catalyze an essential step in the formation of the carcinogenic diol-epoxides of benzo(a)pyrene. The enhancement by BHA of extrahepatic GST activities and nonprotein sulfhydryl levels and possibly, extrahepatic EH activity may be an important factor in the mechanisms by which this antioxidant protects against chemical carcinogenesis. (71 refs)

- 79-5605 Chromosome Aberrations and Sister Chromatid Exchange in Laboratory and Factory Workers and Their Children. (Eng) Funes-Cravioto, F. (Dept. Clinical Genetics, Karolinska Hosp., S-104 01 Stockholm 60, Sweden); Zapata-Gayon, C.; Kolmodin-Hedman, B.; Lambert, B.; Lindsten, J.; Norberg, E.; Nordenskjold, M.; Olin, R.; Swenson, A. *In: Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977. Medical Research Council (Edinburgh, Scotland): 355 pp.; 275-289; 1978.*

A study was made of the frequency of chromosome aberrations and sister-chromatid exchanges (SCE's) in the cultured lymphocytes of 29 women and 6 men working in laboratories where hormone analyses are performed, in 9 women and 7 men working in various chemical laboratories, and in 22 men working in printing factories, where they were exposed to toluene and benzene. Analyses were also made of the lymphocytes of 14 children whose mothers worked in the hormone analysis laboratories during pregnancy. Cultured lymphocytes from all 73 adult subjects had a significantly increased frequency of chromosome aberrations, mainly chromatid and isochromatid breaks, in comparison with 49 control subjects (42 adults and 7 children). An increase of the same magnitude was also found in the 14 children (aged 4 days-11 yr) of 11 women who had worked in the hormone analysis laboratories

during pregnancy. A significant correlation between age and frequency of chromosome aberrations was noted for the exposed and control children, but not for the adults. The frequency of SCE's was significantly increased in a group of 12 technicians working in laboratories performing hormone analysis. Four of the 14 exposed children also had a significantly increased frequency of SCE's. There was a considerable overlap between exposed and control groups with regard to the frequency of chromosome aberrations and SCE's. The cause and biological significance of these findings are not yet known. (24 refs)

- 79-5606** Natulan Induces Forward Mutations to L-Arabinose-Resistance in *Salmonella typhimurium*. (Eng) Pueyo, C. (Catedra de Genetica, Escuela Tecnica Superior de Ingenieros Agronomos, Universidad de Cordoba, Cordoba, Spain). *Mutat Res* 67(2): 189-192; 1979.

The induction of forward mutations from L-arabinose-sensitivity to L-arabinose-resistance in *Salmonella typhimurium* by natulan is reported, and the roles of the excision-repair system and the lipopolysaccharide barrier in the detection of natulan as a bacterial mutagen are discussed. The bacterial strains, as a result of the mutation *araD531*, are sensitive to L-arabinose and are unable to grow in media with L-arabinose and another carbon source. In the absence of liver microsomes (derived from CD1 male mice), natulan was toxic and slightly increased the mutation frequency of strain SV3. When liver microsomes were incorporated into the assay no activity was detected. The excision-repair deficient strain, SV19, was much more sensitive than SV3 with respect to both lethal and mutagenic effects. The mutation frequency of SV19 expressed as $\text{Ara}^r/10^6$, was >200 with a dose of 20 mg/ml of natulan, while that of SV3 was 2.2 in the absence of microsomes. The lowest dose of natulan which doubled the SV19 spontaneous mutation frequency was 5.8 mg/ml. At the highest concentration tested, 30 mg/ml, the spontaneous mutation frequency increased up to 1,000-fold. In strain SV21, which carries a deep-rough mutation and is excision-repair deficient, the enhanced sensitivity to natulan was negated. The mutation frequency was approx 5 for SV21, while it was approx 4,000 for SV19 with 30 mg/ml of natulan in the absence of microsomes. (13 refs)

- 79-5607** Interaction of 4-Methylbenzaldehyde with Rabbit Pulmonary Cytochrome P-450 in the Intact Animal, Microsomes, and Purified Systems. Destructive and Protective Reactions. (Eng) Patel, J. M. (Dept. Pharmacology, Univ. Florida, Gainesville, FL); Wolf, C. R.; Philpot, R. M. *Biochem Pharmacol* 28(13): 2031-2036; 1979.

General mechanisms involved in the partial destruction of rabbit pulmonary cytochrome P-450 by 4-methylbenzaldehyde (4-MBA) are described. About 50% of rabbit pulmonary cytochrome P-450 is destroyed by treatment of the intact animal, microsomes, or systems reconstituted from purified pulmonary monooxygenase components with 4-MBA. The loss of the cytochrome is accompanied by an equimolar loss of heme. The action of 4-MBA requires the presence of NADPH and O_2 and appears to result from cytochrome P-450-catalyzed metabolism. Selective destruction of one of the known forms of rabbit pulmonary cytochrome P-450 does not account for the lack of complete destruction of pulmonary P-450 by 4-MBA; loss of about 50% of each form of the cytochrome occurs in vivo and in reconstituted systems. However, form II is affected to a greater extent than form I when microsomes are incubated with 4-MBA. The portion of the

cytochrome not degraded by 4-MBA appears to be protected by some factor produced from 4-MBA during the incubation. This factor also protects against complete destruction of the cytochrome by cumene hydroperoxide. (28 refs)

- 79-5608** Mutagenic Effects of Styrene and Styrene Oxide. (Eng) Busk, L. (Dept. General Genetics, Univ. Uppsala, S-750 07 Uppsala, Sweden). *Mutat Res* 67(3): 201-208; 1979.

The mutagenicity of styrene and its presumed metabolite styrene oxide (SO) was tested in the *Salmonella*/liver microsome assay using tester strains TA1535, TA1537, TA1538, TA98, and TA100. At 1-10 micromoles (μmol)/plate, SO was mutagenic to TA1535 and TA100, both in the absence and presence of a rat liver microsome system. Styrene, on the other hand, in the concentration range 10^{-3} to $15 \mu\text{mol}$ /plate, was not mutagenic to any of the tester strains, regardless of the presence or absence of a $9,000 \times g$ supernatant of rat liver homogenate. Two differently induced microsomal fractions were used, one induced with Aroclor 1254 and one with another polychlorobiphenyl mixture, Clophen C. Styrene was negative in both systems. Styrene is presumed to be metabolized to SO, and in an attempt to potentiate the possible mutagenicity of styrene, two inhibitors of SO metabolism were added to the homogenates. They were 1,1,1-trichloropropene 2,3-oxide, an inhibitor of epoxide hydratase, and diethyl maleate, an inhibitor of the glutathione conjugation pathway. This did not result in any mutagenic effect of styrene. It is concluded that in the *Salmonella*/liver microsome test, SO is a mutagenic, whereas its presumed precursor in the presence of a metabolizing system is not. This may indicate that when styrene is tested with a rat liver microsome fraction, the concentration of SO is too low for the compound to be detected as a mutagen. (13 refs)

- 79-5609** Styrene Induced Modifications of Some Rat Liver Enzymes Involved in the Activation and Inactivation of Xenobiotics. (Eng) Lambotte-Vandepaer, M. (Lab. Biototoxicology, Catholic Univ. Louvain, Sch. Pharmacy, U.C.L-73.69, 1200 Brussels, Belgium); Bogaert, M. D.; de Meester, C.; Noel, G.; Poncelet, F.; Roberfroid, M.; Mercier, M. *Biochem Pharmacol* 28(10): 1653-1659; 1979.

Male Wistar rats were injected ip with single doses of styrene (10,000, and 500 mg/kg). Its effects on the kinetic parameters of liver microsomal monooxygenases and epoxide hydratase were investigated and compared with those produced by ethylbenzene (EB: 100 mg/kg), the vinyl-saturated analog of styrene, and by phenobarbital (PB: $2 \times 80 \text{ mg/kg}$) and 3-methylcholanthrene (3-MC: $2 \times 40 \text{ mg/kg}$), the classical inducers of those enzymes. The biochemical modifications were correlated with the altered ability of liver homogenates (S-9 fraction) from similarly pretreated rats to activate benzo(a)pyrene (BP) to intermediates mutagenic in *Salmonella typhimurium*. Styrene or 3-MC administration decreased the K_m of BP hydroxylase and aldrin epoxidase; styrene, but not 3-MC, decreased the K_m of styrene oxide hydratase. Neither of the two compounds modified the K_m of styrene epoxidase. Pretreatment of the rats with styrene or 3-MC enhanced the S-9-mediated mutagenicity of BP sevenfold, compared with the mutagenic response mediated by S-9 preparations from control rats. PB and EB did not modify the K_m of the liver enzymes or the liver-mediated mutagenicity of BP. (32 refs)

- 79-5610** Chromosomal Aberrations Induced by Maleic Hydrazide and Related Compounds in Chinese

Hamster Cells In Vitro. (Eng) Nishi, Y. (Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corp., Hatano, Kanagawa 257, Japan); Mori, M.; Inui, N. *Mutat Res* 67(3): 249-257; 1979.

The cytotoxic effects and chromosome aberrations induced by maleic hydrazide (MH) and related compounds were investigated in cultured Chinese hamster (V79) cells. MH was 5-14 times more cytotoxic than potassium MH (K-MH) and diethanolamine MH (DEA-MH) and almost 4.5 times less toxic than hydrazine dihydrochloride (HDC). When the V79 cells were exposed to these compounds for 3 hr, the LD₅₀ values were (in µg/ml) 1,100 (MH), 12,000 (DEA-MH), 20,000 (K-MH), 230 (HDC), and 10,000 (NaCl). MH, K-MH, and DEA-MH, but not HDC or NaCl, caused chromosome aberrations in cultured V79 cells. The max frequencies of aberrant cells in cultures exposed to the compounds for 3 hr were 18% (MH at 1,000 µg/ml), 18% (K-MH at 20,000 µg/ml), and 13% (DEA-MH at 20,000 µg/ml). Max frequencies observed in cultures treated with HDC or NaCl were 10% (HDC at 400 µg/ml) and 5% (NaCl at 10,000 µg/ml). Max frequencies in positive controls were 97% (N-methyl-N'-nitro-N-nitrosoguanidine at 5 µg/ml) and 16% (ethyl methanesulfonate at 400 µg/ml). The frequencies with MH, K-MH, and DEA-MH were 3.25-4.5 times those in untreated control cells. These results suggest that MH, K-MH, and DEA-MH have weak cytotoxicity and positive cytogenetic effects in V79 cells in vitro. (30 refs)

79-5611 Cytogenetic Action of the Antihypertensive Agent Adelphane on Meiotic Cells of *Poecilocus pictus*. (Eng) Jameela (Cytogenetics Lab., Dept. Genetics, Osmania Univ., Hyderabad 500007, India); Subramanyam, S. *Mutat Res* 67(3): 295-299; 1979.

The cytogenetic action of the antihypertensive agent, Adelphane, on the meiotic cells of the Acridid grasshopper, *Poecilocus pictus*, was studied. The drug (0.0014, 0.0053, or 0.0074 mg) was injected between the third and fourth abdominal segments. Gaps, particularly of the chromatid type, and laggards were the only aberrations seen during spermatogonial division. Gaps, breaks, fragments, and translocations were seen during the meiotic division I stages; and numerical anomalies were seen in diplotene, diakinesis, and metaphase I. Lagging of chromosomes or their fragments was seen at all periods and doses. The mitoclastic effects of Adelphane were seen in cells in the second meiotic division, laggards and groupings being the direct results of such action. Stickiness was observed in all periods. Abnormalities in all divisions were most often seen 24 hr after drug administration, and there was generally a reduction in the frequency of aberrant cells from 24 to 72 hr. It is concluded that the effects induced by Adelphane and/or its metabolites are only transitory. (19 refs)

79-5612 Carcinoma of the Renal Pelvis Following the Abuse of Phenacetin-containing Analgesic Drugs. (Eng) Gaakeer, H. A. (Dept. Urology, City Hosp., Dordrecht, Netherlands); De Ruiter, H. J. *Br J Urol* 51(3): 188-192; 1979.

The occurrence of transitional cell carcinoma of the renal pelvis in five women aged 39-73 yr who had taken approx 5-15 kg of phenacetin over a period of 10 yr is reported. Three of the patients had stopped taking the drug before carcinoma was diagnosed: preexisting nephropathy was not an absolute requirement for the subsequent development of a renal pelvic tumor. It is important to

be aware that a urothelial tumor may develop in patients who abuse phenacetin-containing analgesic drugs and that urine cytology in such cases should be performed at regular intervals. If a malignant tumor of the pelvis is suspected, excretion and retrograde pyelography and urine cytology should be sufficient to establish the diagnosis. (25 refs)

79-5613 Recombinogenicity and Mutagenicity of Saccharin in *Saccharomyces cerevisiae*. (Eng) Moore, C. W. (Dept. Biology, Univ. Rochester, Rochester, NY); Schmick, A. *Mutat Res* 67(3): 215-219; 1979.

Diploid yeast (*Saccharomyces cerevisiae*) grown in the presence of a commercial lot of saccharin exhibited reproducible, dose-dependent increases in intergenic and intragenic recombination and mutation. Cells grew to nearly the same titer in media without saccharin and media containing 2 or 20 mg saccharin/ml, although cell viability was somewhat reduced in saccharin-containing media. At the high test dose of 100 mg/ml, titers and cell viability were more markedly lowered. Differences between this study and previous (negative) tests of saccharin in yeast are described. (20 refs)

79-5614 Glass Capillary Gas Chromatographic Detection and Mass Spectral Analysis of Some Hydroxyl Derivatives of Polychlorinated Biphenyls (PCB's). (Eng) Lotjonen, S. (Dept. Pharmaceutical Chemistry, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio, Finland); Ayras, P.; Pyysalo, H. *Finn Chem Lett* (2): 57-60; 1979.

Glass capillary gas-liquid chromatographic (GLC) properties and mass spectra of a number of chlorinated biphenyls are reported. Experimental conditions permitting simultaneous detection of polychlorinated biphenyls and their hydroxylated derivatives by GLC and identification of the latter compounds by mass spectrometry are described. (16 refs)

79-5615 Metabolism of Benzidine to N-Hydroxy-N,N'-diacetylbenzidine and Subsequent Nucleic Acid Binding and Mutagenicity. (Eng) Morton, K. C. (Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI 48201); King, C. M.; Baetcke, K. P. *Cancer Res* 39(8): 3107-3113; 1979.

Benzidine (BZ) metabolism was shown to include the following sequence: BZ → N-acetylbenzidine (ABD) → N,N'-diacetylbenzidine (DABZ) → N-hydroxy-N,N'-diacetylbenzidine → nucleic acid binding. BZ was acetylated in a two-step, acetylcoenzyme A-dependent reaction catalyzed by liver cytosol from hamsters, guinea pigs, mice, and rats (listed in order of decreasing enzyme activity). ABZ and DABZ were identified by thin-layer and high-pressure liquid chromatography and by mass spectrometry. The first acetylation step was more rapid than the second in all species except the guinea pig, in which the rates were equal. ¹⁴C-DABZ was hydroxylated by fortified liver microsomes (hamster > mouse > rat) to yield both N-hydroxy- and 3-hydroxy-¹⁴C-DABZ, which were identified by isotope dilution and/or mass spectrometry. Isotope dilution experiments did not detect the formation of ¹⁴C-N-acetyl-N'-glycolyl-BZ during these incubations. Pretreatment of animals with 3-methylcholanthrene enhanced N- and 3-

hydroxylation in all cases except for 3-hydroxylation by hamsters. Chemically synthesized ^{14}C -N-hydroxy-N-acetyl-N'-acetyl-BZ bound to transfer RNA in the presence of liver cytosol. The binding was catalyzed by an N,O-acyltransferase that varied in the order hamster > rat > mouse. N-Hydroxy-DABZ was mutagenic for *Salmonella typhimurium* TA1538 in the presence of a partially purified N,O-acyltransferase preparation. These data suggest that BZ can be metabolized to reactive derivatives that may contribute to the induction of tumors. (55 refs)

- 79-5616 The In Vitro Binding of 2,2',5,5'-Tetrachlorobiphenyl Metabolites to Rat Liver Microsomal Proteins. (Eng) Hargraves, W. A. (Dept. Pathology, Medical Sch., Univ. Wisconsin, Madison, WI 53706); Allen, J. R. *Res Commun Chem Pathol Pharmacol* 25(1): 33-52;

The in vitro association of ^3H -labeled 2,2',5,5'-tetrachlorobiphenyl (TCB) with the microsomal fraction isolated from rat livers was investigated in a metabolizing system that allows the nature of the binding of the TCB metabolite(s) to the microsomal proteins to be characterized. Control microsomes, capable of only minimal TCB metabolism, had 92% of their total radioactivity associated with membrane lipids, but only 61% of the radioactivity of the phenobarbital-induced microsomes was lipid-bound. The radioactivity per milligram of microsomal protein was the same for both induced and noninduced microsomes; however, very important qualitative differences were found. Only the proteins of the induced system contained a protein(s) (mol wt = 45,000 g/mol) capable of specifically binding a TCB metabolite. This binding required metabolism and was TCB-concentration dependent. The specificity of this association was confirmed by dialysis, and the data could be analyzed by the Scatchard-Klotz equation. These calculations allowed evaluation of the number of binding sites (38 micromoles/g total microsomal protein) and the apparent binding constant (1.4×10^7 liters/mole). These data are consistent with a strong noncovalent interaction of a 2,2',5,5'-TCB metabolite, but they do not exclude the possibility of covalent binding of other nondialyzable metabolites. (44 refs)

- 79-5617 Mechanisms of Action of Carcinogenic Aromatic Amines: An Investigation Using Mutagenesis in Bacteria. (Eng) Scribner, J. D. (Pacific Northwest Res. Foundation, 1102 Columbia St., Seattle, WA 98104); Fisk, S. R.; Scribner, N. K. *Chem Biol Interact* 26(1): 11-25; 1979.

The mutagenicities of several N-acetoxy-N-arylamines, nitroarenes, arylamides, and arylamines were determined in *Salmonella typhimurium* tester strains TA98, TA1538, TA100, TA1535, and TA1537. Three broad classes of mutagenic activity were found: class A, including 2-naphthylamine, produced essentially only base-pair substitution without induction of error-prone repair; class B, including 4-aminobiphenyl, caused considerable induction of error-prone repair, accompanied by a lower level of frame-shifting; class C, including N-acetoxy-2-acetamidofluorene, produced high levels of frame-shifting, with some induction of error-prone repair. Correlation of these results with known reactions of certain aromatic amine derivatives with nucleosides and nucleic acids, and with molecular orbital calculations, suggests that the class A effect is produced by small aromatic groups attached to extranuclear heteroatoms in DNA bases, the class B effect is caused by large aromatic groups attached to extranuclear heteroatoms or by arylamines attached to the C-8 of guanine, and

the class C effect is caused by arylamides attached to the C-8 of guanine, probably rotating into the helix. The data also suggest that the N-acetoxy-N-arylamines are generally useful models for ultimate metabolites derived in vivo, even if the in vivo metabolites do not carry an acetyl group. There was a rough correlation between the sum of the reversions induced in TA98 and TA100 by the N-acetoxy-N-arylamines and their previously determined local carcinogenicities. There was a poor correlation between mutagenicity in any one tester strain and carcinogenicity. (33 refs)

- 79-5618 The Microsomal Activation of Aflatoxin B₁ and 2-(N-Ethylcarbamoyloxymethyl) furan In Vitro Using a Novel Diffusion Apparatus. (Eng) Neal, G. E. (MRC Toxicology Unit, Medical Res. Council Labs., Woodmansterne Road, Carshalton, Surrey SM5 4EF, England); Mattocks, A. R.; Judah, D. J. *Biochim Biophys Acta* 585(1): 134-142; 1979.

The in vitro activation of aflatoxin B₁ (AFB) and 2-(N-ethylcarbamoyloxymethyl) furan (CMF) by liver microsomes from phenobarbital-pretreated adult male Fischer rats was studied. Max binding of DNA was reached at approx 250 nanomoles of AFB and CMF, but the level of binding was 200 picomoles (pmol) of CMF vs 3,000 pmol of AFB per micromole of DNA. The binding of the active microsomal metabolite of CMF to protein was inhibited by GSH, whereas GSH increased the level of binding of CMF to DNA. GSH had no effect on the binding of AFB to protein or DNA. The active metabolite of CMF was able to bind covalently to DNA separated by a membrane barrier from the microsomal site of activation. In the case of AFB, the DNA had to be in physical contact with the microsomal system for its active metabolite to bind covalently. The results suggest that the subcellular site of activation of AFB, unlike that of CMF, may need to be adjacent to the target DNA. This site might be the outer nuclear membrane, or a carrier molecule might exist for the activated AFB metabolite in vivo. (15 refs)

- 79-5619 Histopathology, Autoradiography and Microphotometry of the Rat Liver After Feeding with Aflatoxin B₁. (Eng) Arora, H. L. (Dept. Histopathology, St. George's Hosp. Medical Sch., Tooting, London, England); Butler, W. H. *Indian J Cancer* 15(3): 8-13; 1978.

Sequential changes in the livers of male albino Fischer rats fed 5 ppm aflatoxin B₁ (AFB) for 1-6 wk were studied. After 1 wk of AFB feeding, the architecture of the liver lobule was preserved, but there were areas of focal and individual cell necrosis. After 3 wk, periportal necrosis, extensive proliferation of oval cells, variations in the size of the remaining parenchymal cells, and their nuclei, and increased numbers of mitotic figures were prominent features. After 4.5 wk, focal areas of liver cell necrosis were distributed throughout the liver lobule. The proliferating hyperplastic nodules were of two types: one consisted of small cells having a deeply stained cytoplasm with uniform-sized nuclei and one consisted of larger cells with a vacuolated cytoplasm and bizarre nuclei. These two types of nodules were present in enhanced size and number at 6 wk. The percentage of parenchymal cells labeled with ^3H -thymidine did not differ significantly in control and AFB-fed rats, but the percentage of labeled cells was significantly increased in the hyperplastic nodules compared with that in other parts of the liver. There was increased microphotometric absorptivity of DNA in the periportal area after 6 wk of AFB feeding. DNA absorbance was lower in the small cell nodules than in the large cell nodules. (19 refs)

- 79-5620 Comparison of Aflatoxin B₁ and Aflatoxin G₁ Binding to Cellular Macromolecules In Vitro, In Vivo and after Peracid Oxidation; Characterisation of the Major Nucleic Acid Adducts. (Eng) Garner, R. C. (Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England); Martin, C. N.; Smith, J. R.; Coles, B. F.; Tolson, M. R. *Chem Biol Interact* 26(1): 57-73; 1979.

The binding of [¹⁴C]aflatoxin B₁ (AFB₁) and [¹⁴C]aflatoxin G₁ (AFG₁) to rat liver and kidney cellular macromolecules was compared. The percentage uptake of [¹⁴C]AFG₁ or [¹⁴C]AFB₁ by the liver and kidney after ip administration to Wistar rats (60 µg/100 g) was not significantly different for the two mycotoxins. Max uptake occurred at 2 hr. However, the amount of binding with liver DNA, ribosomal RNA, and protein was different. The greatest difference was found in the amount of binding with ribosomal RNA, which was significantly less for AFG₁. AFG₁ binding to DNA also tended to be lower, but this was significant only at 2 and 24 hr. Protein binding was not significantly different for the two mycotoxins. As reported previously for AFB₁, there was more binding of AFG₁ to nucleic acids than to protein. The loss of radioactivity from liver DNA or ribosomal RNA for both [¹⁴C]AFB₁ and [¹⁴C]AFG₁ appeared to be biphasic, indicating that an enzymic DNA repair process may be operating. In the kidney, AFB₁ appeared to bind more to DNA and protein than AFG₁. Insufficient ribosomal RNA was recovered for accurate determination of binding. In vitro binding studies also showed that less AFG₁ was bound to exogenous DNA after microsomal activation than AFB₁. This difference was not a result of differences in the chemical reactivity of the ultimate electrophilic species, the respective epoxides, since chemical activation studies using 3-chloroperbenzoic acid showed that similar amounts of AFG₁ and AFB₁ were converted to the epoxides and were bound to DNA. According to the distribution coefficients of the two mycotoxins, AFB₁ was more lipophilic than AFG₁, a factor that may be important in determining the weaker carcinogenicity of the latter. Characterization of the major AFG₁-DNA adduct formed in vitro, in vivo, and after peracid oxidation showed it to have the structure trans-9,10-dihydro-9-(7-guanyl)-10-hydroxyafatoxin G₁. This adduct is similar to that obtained from AFB₁ by activation in vivo, in vitro, and after peracid oxidation. (33 refs)

- 79-5621 Sensitivity of Cultured Rat Hepatocytes to Aflatoxin B₁ and Benzo(a)pyrene. (Eng) Schaeffer, W. I. (Dept. Medical Microbiology, Univ. Vermont Coll. Medicine, Given Medical Building, Burlington, VT 05405); Chuang, A. H.; Heintz, N.; Bresnick, E. *In Vitro* 15(6): 437-440; 1979.

The sensitivity of a cloned rat hepatocyte line, RL-PR-C, to aflatoxin B₁ (50 µg/ml) and benzo(a)pyrene (10 µg/ml) was tested as a function of population-doubling level. The cells were much more sensitive to the cytotoxic action of these agents subsequent to 230 population doublings. This sensitivity corresponded to the enhanced inducibility of aryl hydrocarbon hydroxylase activity by 3-methylcholanthrene. (9 refs)

- 79-5622 Biologically Active Phorbol Esters Specifically Alter Affinity of Epidermal Growth Factor Membrane Receptors. (Eng) Shoyab, M. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20205); De Larco, J. E.; Todaro, G. J. *Nature* 279(5712): 387-391; 1979.

The effects of 12-O-tetradecanoylphorbol-13-acetate (TPA) and

related tumor promoters on the interactions between epidermal growth factor and its membrane receptors were investigated. TPA reversibly inhibited the binding of ¹²⁵I-labeled EGF to treated mouse and human cells, but it did not affect the binding of various other ligands to their membrane receptors. It altered the affinity of the receptors for EGF without changing the total number of available receptors per cell. Phorbol esters that stimulate cell growth in culture and have tumor-promoting activity in vivo altered the EGF-receptor affinity, but the biologically inactive derivatives failed to change the affinity of EGF for its receptors. (30 refs)

- 79-5623 Inhibition of Phorbol Ester-accelerated Amino Acid Transport in Bovine Lymphocytes. (Eng) Kensler, T. W. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Wertz, P. W.; Mueller, G. C. *Biochim Biophys Acta* 585(1): 43-52; 1979.

The ability of 12-O-tetradecanoylphorbol-13-acetate (TPA) to modulate the uptake of α-aminoisobutyric acid (AIA) by bovine lymphocytes was studied. TPA effectively stimulated AIA uptake over a 5-hr test period following a 20-min lag period. The response was max with 1-10 nanomolar (nM) TPA. At 0.1 nM, TPA was without effect, and at higher concentrations, eg, 1 mM, TPA diminished this response, presumably due to toxic effects. In general, a good correlation existed between the tumor-promoting activities of a variety of phorbol esters tested and their capacity to rapidly accelerate AIA uptake by bovine lymphocytes. Actinomycin D and cycloheximide, but not cytochalasin B or colchicine, partially antagonized the TPA-stimulated uptake of AIA. This uptake was significantly antagonized by retinoic acid, but the epoxy derivatives of retinoic acid and structurally related analogs were inactive as antagonists. Ouabain antagonized TPA-stimulated uptake only slightly. Comparative studies in lymphocytes showed that TPA elicits a number of metabolic responses that appear to originate at the cell membrane and that these responses are differentially antagonized by retinoic acid, the 5,6-epoxide of retinoic acid, and related retinoid analogs. (22 refs)

- 79-5624 Melittin Shares Certain Cellular Effects with Phorbol Ester Tumour Promoters. (Eng) Mufson, R. A. (Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ., Coll. Physicians and Surgeons, 701 W. 168th St., New York, NY 10032); Laskin, J. D.; Fisher, P. B.; Weinstein, I. B. *Nature* 280(5717): 72-74; 1979.

Melittin (ME), a 26-amino acid polypeptide of known sequence, is a major component of bee venom. Because of its amphipathic character, it can be inserted into phospholipid bilayers and it exhibits surfactant activity. When ME (8 × 10⁻⁷ M) or 12-O-tetradecanoylphorbol-13-acetate (TPA: 2 × 10⁻⁸ M), another amphipathic but structurally unrelated compound, was added to cultures of normal C3H/10T1/2 mouse embryo fibroblasts, there was a two- to threefold enhancement of arachidonic acid and prostaglandin E₂ release 3 hr later. When ME (8 × 10⁻⁷ M) or TPA (1 × 10⁻⁷ M) was added to cultures of C3B16 mouse melanoma cells shortly after plating, there was a 24-hr delay in the onset of melanogenesis and a 66% inhibition of pigment formation. This delay in differentiation was not due to growth inhibition or cytotoxicity, as assayed by cell growth rate, time required to reach confluence, or cell DNA content. When ME (8 × 10⁻⁷ M) or TPA (2 × 10⁻⁸ M) were added to adenovirus-transformed rat embryo cells in soft agar culture to assay anchorage-independent growth, there

was an approx threefold increase in cloning efficiency compared with that of control cultures. ME should be useful for examining whether the pleiotropic effects of phorbol ester tumor promoters are secondary to their membrane effects or whether certain effects are mediated by non-membrane-related events. It will also be of interest to determine whether ME itself has tumor-promoting activity. (20 refs)

- 79-5625** A Tumor-promoting Phorbol Ester Inhibits the Cyclic AMP Response of Rat Embryo Fibroblasts to Catecholamines and Prostaglandin E₁. (Eng) Rochette-Egly, C. (Institut de Recherches Scientifiques sur le Cancer, Boite Postale no. 8, 94 800 Villejuif, France); Castagna, M. *FEBS Lett* 103(1): 38-42; 1979.

The cyclic AMP response of cultured rat embryo fibroblasts to prostaglandin E₁, L-epinephrine, and L-phenylephrine was inhibited by pretreatment with 12-O-tetradecanoylphorbol-13-acetate (TPA, 100 ng/ml). However, there was no evidence for a TPA-mediated linkage of adenylate cyclase to α -adrenergic receptor. (26 refs)

- 79-5626** Tumour Promoter TPA Enhances Transformation of Human Leukocytes by Epstein-Barr Virus. (Eng) Yamamoto, N. (Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Herman-Herder-Strasse 11, 78 Freiburg, W. Germany); zur Hausen, H. *Nature* 280(5719): 244-245; 1979.

The effects of 12-O-tetradecanoylphorbol-13-acetate (TPA) on virus induction in Epstein-Barr virus (EBV) genome-harboring cells and on the EBV-induced transformation of human cord blood lymphocytes were analyzed. In the presence of TPA, cord blood WBC infected by EBV showed a sixfold enhancement in the number of transformed colonies and increased colony size, compared with infected cultures grown without TPA. The optimal TPA concentration was 0.31 nanogram/ml and the max number of colonies was obtained at a virus dilution of 1:4. No transformed lymphoblastoid colonies were observed in cultures treated exclusively with TPA. TPA did not enhance colony formation in one EBV genome-negative cell line or in three EBV-positive lines, although it increased colony formation in a fourth EBV-positive line approx threefold. TPA also increased transformation efficiency in liquid culture systems. The results suggest that TPA acts on transformation steps rather than inducing nonspecific colony-stimulating factors known to promote cell growth in agarose. (20 refs)

- 79-5627** The Surface Structure of 7,12-Dimethylbenz(a)anthracene Transformed C3H/10T1/2 Cells. A Quantitative Scanning Electron Microscopical Study. (Eng) Saxholm, H. J. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway); Reith, A. *Eur J Cancer* 15(6): 843-855; 1979.

The relationship between the oncogenicity of 7,12-dimethylbenz(a)anthracene (DMBA)-transformed mouse embryo (C3H/10T1/2) cells and their surface concentration of long microvilli was studied. The cells developed three types of morphologically altered foci after exposure to DMBA. The types II and III cells showed oncogenic potential, whereas the type I cells remained nononcogenic. Scanning electron microscopy showed that the concentration of

short microvilli increased with increasing cell culture passage for all three types. Only on types II and III cells were long microvilli observed. There was a significant correlation between the oncogenic potential and the presence of long microvilli. This observation may be of value in screening for oncogenic transformation of cells in culture. (15 refs)

- 79-5628** Apurinic Acid Endonuclease Activity from Mouse Epidermal Cells. (Eng) Ludwig, G. (Deutsches Krebsforschungszentrum, Institut fur Biochemie, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Thielmann, H. W. *Nucleic Acids Res* 6(8): 2901-2917; 1979.

An endonuclease activity causing single-strand scissions in depurinated and alkylated viral (PM2) DNA was purified 500-fold from perinatal mouse skin epidermal cells transformed in vitro by 7,12-dimethylbenz(a)anthracene. The enzyme was active only at apurinic/aprimidinic sites, regardless of whether these were produced by heating the DNA at an acidic pH or by alkylation with the ultimate carcinogen MeSO₂OMe. The enzyme was inactive on native DNA, on UV-induced pyrimidine dimers in DNA, and on steric distortions (N-2-fluorenylacetyl residues) by modification of the DNA with the carcinogen (Ac)₂ONFln. The purified enzyme fraction was shown to be free of exonuclease, demethylase, and DNA glycosylase activities specific for bases methylated with MeSO₂OMe or MeNOUr. The enzyme was active in the presence of 1 mM EDTA, but its activity was stimulated threefold by the presence of 3-10 mM MgCl₂. Raising the KCl concentration from 40 to 120 mM in a 5 mM Tris-HCl buffer (pH 7.4) resulted in optimum enzyme activity, but KCl concentrations in excess of 200 mM were completely inhibitory. Optimum activity also occurred in 10-40 mM potassium phosphate buffer (pH 7.4). The enzyme did not bind to diethylaminoethylcellulose, but it was eluted from hydroxyapatite, phosphocellulose, and heparin-cellulose columns by 100-250 mM potassium phosphate. The diffusion constant of the enzyme was determined to be 8.2×10^{-7} cm²/sec, the sedimentation coefficient in linear sucrose gradients approx 2.7S, the mol wt approx 31,000 daltons, and the axial ratio approx 4:1. (40 refs)

- 79-5629** A Comparison of the Capacity of Fetal and Adult Liver, Lung, and Brain to Convert Polycyclic Aromatic Hydrocarbons to Mutagenic and Cytotoxic Metabolites in Mice and Rats. (Eng) Juchau, M. R. (Dept. Pharmacology, Univ. Washington, Sch. Medicine, Seattle, WA 98195); DiGiovanni, J.; Namkung, M. J.; Jones, A. H. *Toxicol Appl Pharmacol* 49(1): 171-178; 1979.

Preparations of S-9 fractions from the fetal brains of rats displayed a high capacity to convert 7,12-dimethylbenz(a)anthracene to metabolites mutagenic to *Salmonella typhimurium* tester strains TA-98, TA-100, and TA-1538. The same tissue was only minimally active or inactive in converting benzo(a)pyrene or N-2-fluorenylacetylacetamide to mutagenic metabolites. Fetal brain tissues of mice were virtually inactive with respect to the bioactivation of each of the three procarcinogens but fetal pulmonary tissues of mice produced mutagen-generating activities that were five- to ninefold above background with respect to 7,12-dimethylbenz(a)anthracene. Fetal hepatic and brain tissues of mice also catalyzed the conversion of each of the three promutagens to cytotoxic intermediates, but this phenomenon was not observed with fetal hepatic or brain tissues of rats. Analysis with high-pressure liquid chromatography demonstrated that brain tissues of fetal mice were very active in converting 7,12-dimethylbenz(a)anthracene to ox-

xygenated metabolites, whereas the fetal brain tissues of rats were only minimally active. The chromatographic patterns observed also indicated that different metabolites were formed in the presence of S-9 fractions from rats vs mice. The data are consistent with the hypothesis that the previously observed species difference in susceptibility to transplacental tumorigenesis by polycyclic hydrocarbons is related to differences in target organ biotransformation of these compounds. (21 refs)

- 79-5630 Transplantation of Hamster Buccal Pouch Carcinoma to Neonatal Hamsters. (Eng) Merk, L. P. (Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA 02115); Shklar, G.; Albright, J. *Oral Surg* 47(6): 533-538; 1979.

The transplantation of 9,10-dimethyl-1,2-benzanthracene-induced Syrian hamster buccal pouch epidermoid carcinomas into syngeneic neonatal hamsters by sc and ip inoculation was studied. All recipients and littermate controls were given rabbit anti-hamster lymphocyte serum (ALS) at the time of tumor injection and thrice weekly thereafter. The controls given ALS showed no evidence of tumor growth or other pathology. The sc transplanted tumors ulcerated within a week and sloughed off, leaving a scar. The ip transplanted tumors grew rapidly in all four animals, involving the pancreas and areas around the spleen and intestines. The degree of organ infiltration was greater at 31 days than at 15 or 21 days. The abdominal tumors were epidermoid carcinomas that were significantly more anaplastic than the original buccal pouch tumors. They were characterized by extensive necrosis and cellular proliferation, with notable pleomorphism and hyperchromatism and an altered nuclear:cytoplasmic ratio. (13 refs)

- 79-5631 Metabolism of 7,12-Dimethylbenz(a)anthracene and Its Methyl-hydroxylated Metabolites: Formation of Phenolic Metabolites at the 2-Positions. (Eng) Chou, M. W. (Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD 20014); Easton, G. D.; Yang, S. K. *Biochem Biophys Res Commun* 88(3): 1085-1091; 1979.

Four 2-phenols were identified as rat liver microsome metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) and its methyl-hydroxylated metabolites 7-hydroxymethyl-12-methylbenz(a)anthracene, 7-methyl-12-hydroxymethylbenz(a)anthracene, and 7,12-dihydroxymethylbenz(a)anthracene. The phenols were identified by their UV-visible absorption and fluorescence spectra and their high-pressure liquid chromatography retention times and by mass spectral analyses. The findings suggest that the presence of the 12-methyl group or the 12-hydroxymethyl group suppresses rather than blocks the microsomal oxygenations at the 1,2 positions of DMBA or its methyl-hydroxylated derivatives. The 2-phenols may be formed as nonenzymatic rearrangement products of the 1,2-epoxide intermediates, although their formation by a direct hydroxylation mechanism cannot be ruled out. (15 refs)

- 79-5632 Changes in Mouse Skin Cyclic Nucleotides During Chemical Carcinogenesis and Tumor Response to Treatment with BCG, L-Dopa and Cyclic DBAMP. (Eng) Busse, E. (Oncological Clinic, Medical Sch., Humboldt-Universitat Berlin, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany); Rose, H.; Riessbeck, K. H. *J Cancer Res Clin Oncol* 94(2): 121-130; 1979.

Changes in mouse skin cyclic nucleotides were studied in male ICR mice treated with topical 9,10-dimethyl-1,2-benzanthracene (DMBA) and subsequently with BCG, L-dopa, and/or dibutyryl cyclic AMP (dbAMP). Papillomas appeared on all DMBA-treated animals within 35-49 days and skin tumors appeared on 73/80 within 105 days. Up to 24 hr after the first application of DMBA, both cAMP and guanosine monophosphate (GMP) levels rose. Later, the cAMP level fell below that of normal tissue. The tumors continued to grow deeper into the tissue and increase in size in 15/15 untreated animals, 14/18 animals treated with BCG, 8/20 animals treated with L-dopa + dbAMP, and 4/20 animals treated with L-dopa, dbAMP, and BCG. The neoplastic growths reached a stationary phase in 4/18 mice given BCG, 7/20 mice given L-dopa + dbAMP, and 5/20 mice given L-dopa, dbAMP, and BCG. Tumor regression was observed in 5/20 animals given L-dopa + dbAMP and 11/20 mice given L-dopa, dbAMP, and BCG. cAMP and GMP levels in the skin of mice that had undergone tumor regression were similar to those in normal animals, whereas the levels in mice that did not respond to treatment were similar to those in untreated animals. In mice given Ehrlich ascites tumor cells im, solid tumors with lowered cAMP:cGMP ratios developed. No tumors developed in 6/30 mice treated with L-dopa, dbAMP, and BCG at the time of tumor inoculation or in 20/30 mice treated similarly prior to tumor inoculation. (27 refs)

- 79-5633 Inhibition of Phorbol Ester-induced Tumor Promotion in Mice by Vitamin A Analog and Anti-inflammatory Steroid. (Eng) Weeks, C. E. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN 37830); Slaga, T. J.; Hennings, H.; Gleason, G. L.; Bracken, W. M. *J Natl Cancer Inst* 63(2): 401-406; 1979.

The chemopreventive potential of a vitamin A analog, TMMP ethyl retinoate [ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl- trans-2,4,6,8- nonatetraenoate; Ro 10-9359], and/or an anti-inflammatory steroid, fluocinolone acetonide [6 α ,9 α -difluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal; FA], was studied in a two-stage carcinogenesis system. The phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was used as the tumor promoter in a 7,12-dimethylbenz(a)-anthracene (DMBA)-initiated mouse skin system. Two stocks of female mice, CD-1 and Sencar, which differ in their degrees of sensitivity to skin carcinogenesis, were used. A dose-dependent inhibition of carcinogenic expression, as determined by a decreased number of papillomas per animal, was observed in each mouse stock with the use of FA or Ro 10-9359 alone. When FA and Ro 10-9359 were given together, the decrease in tumor incidence was enhanced. FA effectively inhibited tumor formation in the sensitive mouse stock, even when the steroid was given 1 day prior to TPA treatment under conditions of unusually high doses of initiator (DMBA) and/or promoter (TPA). These results suggest that both anti-inflammatory steroids and retinoids inhibit tumor promotion and can be effectively used as a combination regimen for an increased chemopreventive response. (49 refs)

- 79-5634 Tumorigenicity of the Diastereomeric Benz(a)anthracene 3,4-diol-1,2-epoxides and the (+) and (-) Enantiomers of Benz(a)anthracene 3,4-Dihydrodiol in Newborn Mice. (Eng) Wislocki, P. G. (Merck, Sharp & Dohme Res. Labs., Rahway, NJ 07065); Buening, M. K.; Levin, W.; Lehr, R. E.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *J Natl Cancer Inst* 63(1): 201-204; 1979.

The tumorigenicity of benz(a)anthracene (BA), the (+)- and (-)-enantiomers of trans-3,4-dihydroxy-3,4-dihydrobenz(a)anthracene (BA 3,4-dihydrodiol), and the racemic diastereomers of the BA 3,4-diol-1,2-epoxides [ie, either or both of the diastereomeric 1,2-epoxides derived from BA 3,4-dihydrodiol in which the epoxide oxygen is cis (diol epoxide-1) or trans (diol epoxide-2) to the benzylic 4-hydroxyl group] was examined in newborn Swiss-Webster mice. The mice were inoculated ip with 280 nanomoles (nmol) of one of the test compounds in divided doses: 40 nmol within 24 hr of birth, 80 nmol at 8 days of age, and 160 nmol at 15 days of age. The experiment was terminated when the animals were 26 wk old. Diol-epoxide-2 was the most potent compound tested. All animals treated with diol-epoxide-2 developed pulmonary tumors, with an av of 13.3 tumors per mouse. Diol-epoxide-1 produced pulmonary tumors in 42% of the mice with an average of only 0.56 tumor per mouse. The (-)-enantiomer of BA 3,4-dihydrodiol with [3R,4R] absolute stereochemistry was the second most tumorigenic derivative of BA tested; it produced pulmonary tumors in 71% of the mice with an av of 1.88 tumors per mouse. BA and the (+)-enantiomer of BA 3,4-dihydrodiol had little or no tumorigenicity at the dose tested. A comparison of the av number of pulmonary tumors per mouse revealed that diol-epoxide-2 was about 30-fold more tumorigenic than diol-epoxide-1, 8-fold more tumorigenic than (-)-BA 3,4-dihydrodiol, and >85-fold more tumorigenic than BA. These data indicate that in newborn mice, BA 3,4-dihydrodiol and a BA 3,4-diol-1,2-epoxide are proximate and ultimate carcinogenic metabolites of BA, respectively. (22 refs)

79-5635 Distribution of ^3H -7,12-Dimethylbenz(a)anthracene in the Rat Neuroendocrine System. (Rus) Anisimov, V. N. (Lab. Endocrinology, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Aleksandrov, V. A. *Vopr Onkol* 25(6): 84-88; 1979.

The effects of the neuroendocrine system on the carcinogenicity of polycyclic aromatic hydrocarbons was evaluated. Random-bred rats were inoculated iv with a mixture of unlabeled 7,12-dimethylbenz(a)anthracene (DMBA: 15 mg/kg) and ^3H -DMBA (0.05 mCi/kg). Rats were sacrificed 30 min or 3, 6 or 12 hr later, and the distribution of ^3H -DMBA in different tissues and organs was determined. At 30 min postinoculation, there was a max accumulation of label in the liver, and the radioactivity in the endocrine glands was significantly greater than that in muscle tissue. At 3 hr postinoculation, there was a significant accumulation of label in the adrenals. Label accumulation in the mediobasal hypothalamus at 30 min and at 6 and 12 hr postinoculation was significantly greater than that in the cerebral cortex and dorsal hypothalamus. (26 refs)

79-5636 Collagen Synthesis in Capsules Surrounding Dimethylbenzanthracene-induced Rat Breast Tumors and the Effect of Pretreatment with β -Aminopropionitrile. (Eng) Cohen, I. K. (Dept. Surgery, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA 23298); Moncure, C. W.; Witorsch, R. J.; Diegelmann, R. F. *Cancer Res* 39(8): 2923-2927; 1979.

Collagen and total protein synthesis within the parenchyma and capsule of dimethylbenzanthracene (DMBA)-induced Sprague-Dawley rat breast tumors was compared, and the findings were correlated with tumor histology. In addition, an attempt was made to determine if alterations in the collagenous stroma by inhibition

of collagen cross-linking with β -aminopropionitrile (BAPN) would inhibit capsule formation and allow the tumor to metastasize. Collagen synthesis was increased over threefold in the tumor capsules compared with that in the parenchyma and over sixfold compared with that in normal breast connective tissue. Increased collagen synthesis was independent of the rate of tumor growth and final tumor size. Pretreatment of animals with BAPN caused an 82% decrease in tumor formation and a significant reduction in tumor volume (approx 0.4 cm³) compared with controls (approx 10 cm³). The few small tumors that did develop in the lathyrin animals had increased collagen synthesis in the interior tumor stroma and reduced collagen synthesis in the tumor capsule. These findings suggest that the collagenous capsule surrounding DMBA-induced tumors functions as a physical barrier to protect the tumors from the immune system of the host. The apparent antitumor effects of BAPN may be due to its immunopotential and/or cytotoxic actions. (12 refs)

79-5637 Estradiol Binding to Nuclear Receptors in Human Breast Cancer Tissue (MCF-7 Cell Line) and in Dimethylbenz(a)anthracene-induced Mammary Carcinoma. (Eng) Geier, A. (Inst. Endocrinology, Chaim Sheba Medical Center, Tel-Hashomer, Israel); Cocos, M.; Ginzburg, R.; Haimsohn, M.; Lunenfeld, B. *J Clin Endocrinol Metab* 49(1): 34-39; 1979.

Nuclear estradiol receptors (NR's) were measured in human breast carcinoma tissue (cell line MCF-7) and in dimethylbenz(a)anthracene-induced rat mammary carcinomas by an assay that makes use of the fact that, at low salt concentration, the NR is bound to particles (chromatin) and can be separated from the soluble components that contain proteolytic activity. R degradation by intracellular proteases was avoided by repeated washing of the particulate-bound R. Thus, the amount of occupied NR's (bound by endogenous estrogen) could be measured by exchange at 30 C, and the amount of unoccupied R's could be measured at 4 C. R's were measured by a single saturating dose of 7.5 nanomolar [^3H]estradiol with or without a 100-fold excess of diethylstilbestrol to estimate the amount of nonspecific binding. In mammary tumors from castrated rats, unoccupied R's were found in the cytoplasm. In the nucleus, neither occupied nor unoccupied R's could be detected. Thirty min after injection of estradiol, unoccupied estradiol R's were no longer detected in the cytoplasm. However, 35-50% of the cytoplasmic R's detected in the castrated rats were found as occupied NR's. Before exposure to estradiol, MCF-7 cells contained only unoccupied nuclear and cytoplasmic R's. After a 1-hr exposure to estradiol, only occupied NR's were found. The total amounts of R's before and after treatment were similar. Nuclear and cytoplasmic estradiol R's were measured in 44 human breast tumors. Ten tumors contained neither cytoplasmic nor NR's. In 29/34 patients whose tumors contained cytoplasmic R's, unoccupied NR's were present. Occupied NR's were found in 21/34 of these tumors, in the younger as well as the older patients. However, the latter contained higher levels of cytoplasmic R's. These findings indicate that the presence of occupied NR's in these tumors may depend on various factors, including the circulating levels of estradiol, tumor cytoplasmic R levels, and the translocative ability of the cytoplasmic R. (20 refs)

79-5638 Effect of Microsomal Preparations and Induction on Cytochrome P-450-dependent Monooxygenases in Fetal and Neonatal Rat Liver. (Eng) Cresteil, T. (Laboratoire de Biochimie, CHU Necker-Enfants Malades, 156 rue de Vaugirard, 75730 Paris Cedex 15, France); Flinois, J. P.; Pfister, A.; Leroux, J. P. *Biochem Pharmacol* 28(13): 2057-2063; 1979.

The sedimentation behavior of fetal and neonatal Sprague-Dawley rat liver microsomes was determined with the use of an EDTA-containing buffer, which allowed better recovery of a less-contaminated microsomal fraction. The specific cytochrome P-450 content and related catalytic activities in the 105,000 g pellet of fetal and neonatal liver were thus much higher than those usually reported, but molecular catalytic activities were comparable to those of adults. The transplacental inducing effects of phenobarbital (PB) and 3-methylcholanthrene (3-MC) on the monooxygenase system were studied in microsomes prepared by the modified procedure and compared with results obtained in a crude liver homogenate. 3-MC induced a net biosynthesis of cytochrome P-450 in fetal liver, whereas PB produced only a premature transformation of rough into smooth endoplasmic reticulum, which decreased the contamination of the 105,000 g pellet by ribosomal protein. As a result, the specific cytochrome P-450 level in the microsomal fraction appears to be increased by PB, although there is no true induction of the monooxygenase system in near-term rat fetuses. (40 refs)

- 79-5639 Methylcholanthrene-induced Tumors in Resistant and Sensitive Jensen Sarcoma Rats. I. Effect of Fresh Prepared MC Emulsion. (Eng) Lupu, A. (Oncological Inst. Bucharest, Piata Kogalniceanu 7, ET2, Ap 4, Sector 6, Bucharest, Romania); Corneci, I.; Fadei, L. *J Cancer Res Clin Oncol* 94(2): 115-119; 1979.

The effect of 20-methylcholanthrene (20-MC: 10 mg, sc or im, followed in most cases by a second injection 74 days later) on the development of sarcomas in Jensen sarcoma-sensitive (S) and -resistant (R) Wistar and Long-Evans rats was studied. Tumors developed in 1/2 R and 1/2 S rats after 10 mg 20-MC and in 14/22 R rats and 7/19 S rats after 20 mg 20-MC. Tumors occurred 105-206 days postinjection at the site of the injection, and they evolved within 21-63 days. Histologically, fibroblastic sarcomas predominated. One of the 20-MC-induced sarcomas was transplanted from an R to an R rat and then to an S rat. It strongly immunized receptive rats against this tumor and also against the Jensen sarcoma. Antigenicity was maintained up to the 10th passage. (12 refs)

- 79-5640 Increased Integration of Viral Genome Following Chemical and Viral Treatment of Hamster Embryo Cells. (Eng) Casto, B. C. (Biotech, Inc., 2910 MacArthur Blvd., Northbrook, IL 60062); Miyagi, M.; Meyers, J.; DiPaolo, J. A. *Chem Biol Interact* 25(2/3): 255-269; 1979.

Treatment of hamster embryo cells with diverse classes of chemical carcinogens enhanced transformation by a carcinogenic simian adenovirus, SA7. Virus-transformed foci selected from plates pretreated with 3-methylcholanthrene (MCA), methyl methanesulfonate (MMS) or 7,12-dimethylbenz(a)anthracene (DMBA) and established as cell lines in culture contained equivalent amounts of SA7-viral genome. However, hamster embryo cultures treated with MMS or nickel sulfate had increased amounts of SA7 DNA integrated into cellular DNA when examined 2-9 days after chemical treatment and viral inoculation. An increased uptake of SA7 DNA was demonstrated in hamster cells treated with MMS during DNA repair synthesis in cells restricted in scheduled DNA synthesis by amino acid deprivation; addition of virus after the repair period did not result in an increased integration of viral DNA. These data suggest that the enhancement of viral oncogenesis by chemical carcinogens or mutagens may be

related to the formation of additional attachment sites in cellular DNA for insertion of viral DNA, thereby increasing the probability of viral transformation. (29 refs)

- 79-5641 Ascites Tumors in CBA Mice. Characterization of Two New Tumors, a Carcinoma and a Sarcoma in Solid and Ascites Form, with Regard to Cell Surface Properties and Transplantability. (Eng) Ryd, W. (Inst. Pathology, I, Univ. Goteborg, Goteborg, Sweden); Hagmar, B. *J Cancer Res Clin Oncol* 94(2): 185-199; 1979.

Two ascites tumors in syngeneic CBA mice (MCB 21-AA and MCB 31-AA) were studied, as were their solid progenitors, a sarcoma (MCB 21-SS) and a squamous cell carcinoma (MCB 31-SC) induced by gastric feeding of 20-methylcholanthrene. The ascites tumors showed differences in cell size, aggregatability, and growth rate. A certain number of tumors of each type demonstrated a PAS-positive "corona" at the periphery. MCA 21-SS and -AS (solid ascites tumor) were only weakly affected by concanavalin A (Con A), but they were heavily agglutinated by wheat germ agglutinin (WGA). MCB 21-AA was somewhat agglutinated by WGA but it was insensitive to Con A. MCB 31 showed the same pattern, but 31-SC was less agglutinable by WGA than 31-AS. Both ascites tumors showed higher electrophoretic mobilities than AS and SS/SC cells, the difference being greatest for 31-AA. MCB 21-AS and -SS and 31-AS had low thromboplastic activities, whereas MCB 31-SC had a high activity. MCB 21-SS, -AA, and 31-AA were hypotetraploid, and 31-SC was hypertetraploid. However, all lines showed considerable variation in chromosome number and chromosome markers. Suspensions of tumor cells were injected sc, ip, or iv into syngeneic and allogeneic mice. Relatively high cell doses were required for transplantation, even in syngeneic mice. Whole body x-radiation (300 rads) decreased the number of cells needed for transplantation ip and iv, except in the case of MCB 31-SC. Pulmonary metastases were common in animals dying following iv tumor injection; extrapulmonary metastases were rare. (30 refs)

- 79-5642 Lung Tumors in Mice Suckled by 3-Methylcholanthrene-treated Mothers. (Eng) Kinoshita, K. (Dept. Pathology, Chest Disease Res. Inst., Kyoto Univ, Kyoto 606, Japan); Takahashi, G.; Yasuhira, K. *Bull Chest Dis Res Inst Kyoto Univ* 12(1/2): 10-16; 1979.

Lung tumor incidence was studied in ICR mice suckled by mothers receiving the potent carcinogen 3-methylcholanthrene (3-MC: 5 mg in 0.5 ml sesame oil) by stomach tube on days 2 and 4 after delivery. Lung tumors were found in 28/46 male progeny and in 10/36 female progeny. Histologically, the tumors were adenomas and adenocarcinomas. No tumors developed in mice suckled by untreated mothers. 3-MC in milk and lung tissue was measured radiometrically to confirm its transfer via milk to the suckling mice. The amount of carcinogen in the lungs of the sucklings was <13.5 nanograms/mg of wet tissue, which agreed with the value obtained previously in fetal lungs when pregnant mice near term were treated po with 5 mg 3-MC. When analyzed by gas chromatography-mass spectrometry, ethanol-soluble fractions of milk from the stomachs of suckling mice contained the parent carcinogen and its 2-hydroxy, dehydro, and 1,2-dihydroxy derivatives. These metabolites are all carcinogenic in mice. (24 refs)

- 79-5643 Effect of Delay in Administration of 13-cis-Retinoic Acid on the Inhibition of Urinary Bladder Car-

cinogenesis in the Rat. (Eng) Becci, P. J. (Life Sciences Div., IIT Res. Inst., Chicago, IL 60616); Thompson, H. J.; Grubbs, C. J.; Brown, C. C.; Moon, R. C. *Cancer Res* 39(8): 3141-3144; 1979.

The effect of a delay of 13-cis-retinoic acid (RA) treatment on the inhibition of N-butyl-N-(4-hydroxybutyl) nitrosamine (OH-BBN)-induced urinary bladder carcinogenesis was studied in male Fischer 344 rats. Animals received a total of 1,200, 1,800, or 2,400 mg OH-BBN by gastric intubation over a period of 6 wk (100, 150, or 200 mg 2x/wk). At 1, 5, and 9 wk after the last OH-BBN dose, animals were started on a diet supplemented with RA (240 mg/kg of laboratory chow) or continued on laboratory chow. Animals were killed at 1 yr after the first carcinogen intubation for histological evaluation of the bladder. Feeding of RA reduced the incidence, av number, and severity of transitional cell carcinomas and of hyperplasia and cellular atypia. Furthermore, even a 9-wk delay in starting the RA feeding did not diminish its ability to inhibit bladder carcinogenesis. (10 refs)

79-5644 Interaction of Retinoic Acid and 3-Methylcholanthrene on the Fine Structure of Mouse Prostate Epithelium In Vitro. (Eng) Muller-Salamin, L. (Strangeways Res. Lab., Wort's Causeway, Cambridge CB1 4RN, England); Matter, A.; Lasnitzki, I. *J Natl Cancer Inst* 63(2): 485-495; 1979.

The effects of 3-methylcholanthrene (3-MC) and retinoic acid (RA) on the ultrastructure of AKR mouse prostate epithelium in organ culture were correlated with changes in cell proliferation. In intact glands before explantation, the epithelial cytoplasm showed concentric flat or globular cisternae of endoplasmic reticulum (ER) in both supranuclear and basal areas, a well-developed Golgi complex, secretory vesicles, and numerous microvilli at the luminal surface. After explantation, the cytoplasmic organelles, particularly the ER, regressed and tonofilaments appeared. The regression was largely prevented by RA. 3-MC induced considerable epithelial hyperplasia and squamous metaplasia. The ultrastructure of the newly formed cells revealed a complete loss of ER, Golgi apparatus, secretory vesicles, and microvilli, with the appearance of bundles of tonofilaments and a striking increase in the number of desmosomes. Administration of RA to explants pretreated with the carcinogen partially reversed the hyperplasia and squamous metaplasia. The tonofilaments disappeared and the number of desmosomes greatly decreased, whereas the ER, Golgi complex, secretory vesicles, and microvilli were largely reestablished. Planimetric measurements of the alveolar epithelium showed that the squamous transformation and its partial reversal by RA coincided with the rise and decline of epithelial hyperplasia. The data suggest that the restoration of secretory differentiation by RA was responsible for the initial breakdown of the hyperplastic epithelium, whereas the lowering of DNA synthesis by RA prevented further hyperplasia and kept all replication within normal limits. (27 refs)

79-5645 Chromosome Abnormalities Produced in Human Lymphocytes by Organic Extracts from River Water. (Eng) Doloy, M. T. (Departement de Protection, Section de Radiopathologie, Centre d'Etudes Nucleaires, B.P. No. 6, 92260 Fontenay-aux-Roses, France); Le Go, R.; Hardy, M.; Reillaudou, M. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 311-315; 1978.

Chromosome abnormalities caused by organic extracts in river water were investigated in human lymphocytes in order to determine optimal experimental conditions for increasing the effect observed while maintaining mitotic activity. Particular emphasis was placed on the influence of the pollutant concentration in the culture and the pollutant-lymphocyte contact time. Chloroform extracts of organic substances from river water were used in a concentration of 200 µg/ml nutritive medium after complete evaporation. As a reference pollutant, 3,4-benzopyrene (BP) in dimethyl sulfoxide was introduced into the cultures at concentrations of 1 or 10 µg/ml. The standard technique involved culturing the lymphocytes for 2-3 days, with the micropollutant added at the beginning of culture time; or 4-5 day lymphocytes received the micropollutant after 24 hr of incubation. The long-lasting culture technique involved isolation of the lymphocytes, and incubation for 4 or 7 days at 37 C. The cells had a very low mitotic index because a low concentration of phytohemagglutinin was used in the medium. Three days after mitotic stimulation, the cells were treated according to standard methods for chromosomal observations. The cultures inoculated with pollutants were compared with control cultures. In control cultures, the frequency of chromosomal abnormalities was similar for all culture methods. More abnormalities were observed in the BP-treated cultures with a 4-day latent period than in the 2 or 3-day classical cultures. More abnormalities were observed in 3-day cultures than in 2-day cultures in which the same pollutant had been introduced. Similarly, more abnormalities were observed in the long-lasting cultures than in the 3-day classical cultures. In the 3-day cultures, a greater percentage of pollutants showed a significant effect, and this effect was more evident in the long-lasting cultures. Thus, the long-lasting culture technique is recommended for studies on the cytogenetic effects of pollutants. (no refs)

79-5646 Ellipticines as Potent Inhibitors of Microsomes-dependent Chemical Mutagenesis. (Eng) Lesca, P. (Laboratoire de Pharmacologie et de Toxicologie Fondamentales, 205 route de Narbonne, 31078 Toulouse Cedex, France); Lecoite, P.; Paoletti, C.; Mansuy, D. *Chem Biol Interact* 25(2/3): 279-287; 1979.

The inhibitory effects of ellipticine (E), 9-hydroxyellipticine (9-OHE), 9-fluoroellipticine (9-FE), and 7,8-benzoflavone (7,8-BF) on the mutagenicity of a large number of compounds were investigated. Aromatic amines, polycyclic hydrocarbons, fungal toxins, and azo compounds were used as mutagens in Ames bacterial assays with and without rat microsomal cytochrome P-450 monooxygenases (S9 mix). Most of the chemicals tested were mutagenic only in the presence of the S9 mix. E and 9-OHE exhibited weak mutagenicity in the presence of the S9 mix; 9-FE and 7,8-BF were not mutagenic with or without the mix. The presence of an OH or F group at position 9 decreased or suppressed the mutagenicity. 9-OHE greatly inhibited the mutagenicity of the activatable compounds tested, sometimes resulting in complete suppression of mutagenicity. In all cases except that of aflatoxin B₁, the amount of 9-OHE that decreased mutagenicity by 50% was lower than the amount of mutagen used in the test. With respect to benzo(a)pyrene-induced mutagenesis, 9-OHE and 9-FE were more potent inhibitors than E. 9-OHE was 10 times more potent in inhibiting the mutagenicities of benzo(a)pyrene, aflatoxin B₁, 3-methylcholanthrene, and ethidium bromide than 7,8-BF. It appears possible to design derivatives of E that lack mutagenicity in themselves but may be useful in vivo as potent inhibitors of chemically induced mutagenesis. (21 refs)

79-5647 The Role of Cytochrome P-450 Forms in 2-Aminoanthracene and Benz(a)pyrene Mutagenesis.

(Eng) Norman, R. L. (Dept. Biochemistry, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Muller-Eberhard, U.; Johnson, E. F. *Biochem Biophys Res Commun* 89(1): 195-201; 1979.

The role of four forms (2,3,4, and 6) of cytochrome P-450 from rabbit liver in the metabolic activation of two suspected carcinogens, 2-aminoanthracene (AA) and benzo(a)pyrene (BP), was studied using *Salmonella typhimurium* strain TA98. The number of bacterial revertants increased in a linear fashion for both AA and BP mutagenesis with increasing incubation time at 37 C. Metabolic activation of both compounds to mutagens increased as a linear function of the concentrations of form 4 to 6 up to 100 picomoles of cytochrome P-450 per incubation. Thus, the amount of cytochrome P-450 was rate-limiting. Form 4 produced 10-30 times more revertants with AA than a control incubation in which cytochrome P-450 was omitted. BP mutagenesis appeared to be catalyzed almost exclusively by form 6, which produced 6-15 times the number of revertants observed in control incubations. In both cases, the other forms of cytochrome P-450 produced at most three times more revertants than control incubations. The results indicate that specific cytochrome P-450 forms preferentially activate particular mutagens. (30 refs)

79-5648 Insectan Aryl Hydrocarbon Hydroxylase Generates Benzo(a)Pyrene Metabolites That Bind to Protein and DNA. (Eng) Anderson, R. S. (Donald S. Walker Lab., Sloan-Kettering Inst. Cancer Res., 145 Boston Post Rd., Rye, NY 10580). *Comp Biochem Physiol [C]* 63(1): 17-20; 1979.

A study suggesting that insectan microsomal oxidases can metabolically activate carcinogenic polycyclic hydrocarbon is reported. Oxidation of benzo(a)pyrene by *Spodoptera eridania* microsomal enzymes generated metabolites that bound to biological macromolecules. Aryl hydrocarbon hydroxylase induction by the topical application of polychlorinated biphenyls in larvae stimulated benzo(a)pyrene metabolite binding. Inhibition of aryl hydrocarbon hydroxylase activity decreased metabolite binding. (31 refs)

79-5649 Mutagenesis of Certain Benzo(a)pyrene Phenols In Vitro Following Further Metabolism by Mouse Liver. (Eng) Owens, I. S. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Development, NIH, Bethesda, MD 20014); Koteen, G. M.; Legraverend, C. *Biochem Pharmacol* 28(10): 1615-1622; 1979.

The consequences of the metabolic activation of certain phenols of benzo(a)pyrene (BP) were examined, along with how conjugation reactions may alter these effects. Phenols produced enzymatically were of particular interest, especially 3-hydroxybenzo(a)pyrene (3-OH-BP). Low concentrations of 1-OH- and 3-OH-BP in the presence of NADPH and the liver S-9 fraction from 3-methylcholanthrene (3-MC)-treated C57BL/6N mice were up to three times more mutagenic than BP in the *Salmonella typhimurium* LT₂ tester strain TA98. The level of mutagenicity rose with increasing phenol or S-9 protein concentration. In this system, 9-OH-BP was slightly mutagenic, but 2-OH-, 7-OH-, and 12-OH-BP were not mutagenic at low concentrations. The S-9 fraction from 3-MC-treated DBA/2N mice or phenobarbital-treated C57BL/6N mice did not support significant levels of mutagenesis. The high level of mutagenicity by 1-OH- or 3-OH-BP was inhibited by α -naphthoflavone but not by metyrapone, 1,2-epoxy-3,3,3-trichloropropane, or glutathione. The substrate for

uridine diphosphate (UDP)-glucuronosyltransferase, UDP-glucuronic acid, prevented more than half of the mutagenicity caused by the further metabolism of 1-OH- and 3-OH-BP. The combination of UDP-glucuronic acid and UDP-N-acetylglucosamine provided an even higher level of protection. The addition of the substrate for sulfotransferase(s), 3'-phosphoadenosine 5'-phosphate sulfate, also prevented about half of the mutagenesis caused by 1-OH- or 3-OH-BP. (40 refs)

79-5650 Mutation of Human Cells by Kerosene Soot. (Eng) Skopek, T. R. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Liber, H. L.; Kaden, D. A.; Hites, R. A.; Thilly, W. G. *J Natl Cancer Inst* 63(2): 309-312; 1979.

A human lymphocyte mutation assay was used to determine the mutagenicity of a methylene chloride extract of kerosene soot and two components of the extract, benzo(a)pyrene (BP) and cyclopenta(cd)pyrene (CP). The polycyclic aromatic hydrocarbon fraction of kerosene soot induced forward mutations in human diploid lymphoblasts when coincubated with a Sprague-Dawley rat liver postmitochondrial supernatant. BP was not mutagenic at the concentration found in the soot extract (0.52 μ g/ml), although it was active at higher concentrations. The amount of CP present could account for approx 8% of the total mutations observed with the soot. The results were compared with data obtained previously in a similar mutation assay in *Salmonella typhimurium*. The protocol described permits the facile assay of mutation at the *hprt* locus in human lymphoblasts; this mutation is induced by compounds or complex mixtures requiring mixed-function oxygenase activity for metabolism to genetically active derivatives. (30 refs)

79-5651 Metabolism of Benzo(a)pyrene in Hamster Embryo Cells. Effect of the Concentration of Benzo(a)pyrene on Its Metabolism. (Eng) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Hirakawa, T.; Takayama, S. *Chem Biol Interact* 25(2/3): 177-188; 1979.

The metabolism of benzo(a)pyrene (BP) by hamster embryo cells was studied. The production of water-soluble metabolites, shown to be conjugates with glucuronic acid, depended on BP concentration. With increased BP concentration the amount of glucuronic acid conjugates increased, but the proportion of conjugates in BP or its metabolites present in the medium decreased. The metabolites extracted with ethylacetate were *trans*-7,8-dihydrodiol-BP (7,8-dihydrodiol) and *trans*-9,10-dihydrodiol-BP (9,10-dihydrodiol), but large peaks of phenolic metabolites were found by high pressure liquid chromatography (HPLC) after digestion of the medium with β -glucuronidase. Therefore, BP was metabolized to oxygenated forms, and of these, most of the phenolic metabolites and parts of the dihydrodiols were conjugated with glucuronic acid. The proportions of dihydrodiols to phenols, estimated by HPLC after β -glucuronidase digestion, decreased when the BP concentration was decreased. The results suggest that dihydrodiols are less readily glucuronidated than phenols and so may be metabolized further to metabolites other than glucuronic acid conjugates. (24 refs)

79-5652 Metabolism and Toxicity of Benzo(a)pyrene-4,5-oxide in the Isolated Perfused Rat Liver. (Eng) Smith, B. R.

(Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709); Bend, J. R. *Toxicol Appl Pharmacol* 49(2): 313-321; 1979.

[G-³H]benzo(a)pyrene-4,5-oxide ([G-³H]BP-4,5-oxide) in isolated perfused rat livers was metabolized predominantly to conjugates (mainly thioether derivatives) and to a lesser extent to the dihydrodiol. The metabolites were released from the livers into the vascular circulation, but biliary excretion was the major route of removal of the metabolic products. BP-4,5-oxide caused periportal damage and was covalently bound to tissue DNA, RNA, and protein. BP-4,5-oxide metabolism in the isolated liver and in intact rats was qualitatively and quantitatively similar. (40 refs)

79-5653 Deoxyribonucleic Acid Binding of 3-Hydroxy- and 9-Hydroxybenzo(a)pyrene Following Further Metabolism by Mouse Liver Microsomal Cytochrome P₁-450. (Eng) Owens, I. S. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014); Legraverend, C.; Pelkonen, O. *Biochem Pharmacol* 28(10): 1623-1629; 1979.

Since 3-hydroxy- and 9-hydroxybenzo(a)pyrene (3-OH- and 9-OH-BP) are the major primary metabolites of benzo(a)pyrene (BP) and since certain phenols are strong mutagens, the DNA-binding activity of these compounds was investigated, along with the effects of various modifiers on binding. In the presence of NADPH and microsomes from 3-methylcholanthrene (3-MC)-treated C57BL/6N mice, [³H]3-OH-BP was metabolized to reactive intermediates that covalently bound to deproteinized salmon sperm DNA in vitro. Enzymatically digested DNA, containing bound [³H]3-OH-BP derivatives, generated an elution profile upon Sephadex LH20 chromatography that resembled similar chromatograms with [³H]BP. All peaks resulting from [³H]BP activation appeared to be represented in [³H]3-OH-BP activation, except that several peaks that emerged near the end of the eluting gradient of methanol and water were much reduced. Notably, a peak designated E that is attributed to BP-7,8-diol-9,10-oxide binding in [³H]BP incubations, was also prominently represented in incubations with [³H]3-OH-BP. Radioactivity in all of these peaks was inhibited if one-seventh the concentration of 1-OH-BP was included in the incubation with [³H]3-OH-BP. Microsomes from 3-MC-treated DBA/2N mice caused insignificant binding. Uridine diphosphate (UDP)-glucuronic acid markedly reduced all peaks except E, and 1,2-epoxy-3,3,3-trichloropropane reduced all peaks except C and E. 9-OH-BP was further metabolized to DNA binding species by microsomes from either 3-MC-treated DBA/2N or C57BL/6N mice. UDP-glucuronic acid prevented about 50% of the binding with microsomes from DBA/2N mice but not with microsomes from C57BL/6N mice. UDP-glucuronic acid did prevent binding in some of these same peaks when [³H]-BP was the starting substrate with microsomes from C57BL/6N mice. UDP-glucuronic acid did not prevent binding in peak E in incubations with [³H]BP or [³H]3-OH-BP. (26 refs)

79-5654 Interaction of Benzo(a)pyrene and a Hyperplastic Agent in Epidermal Nuclear Enlargement in the Mouse. A Dose-Response Study. (Eng) Ingram, A. J. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey, England). *Chem Biol Interact* 26(1): 103-113; 1979.

The effects of various dose levels of benzo(a)pyrene (BP: 0.4-2,500

µg/ml on nuclear size in To strain mouse interfollicular epidermis were determined over a 3-day period. Topical application of BP was made with or without croton oil (CO: 0.1% or 0.5%) in acetone, toluene, or methyl ethyl ketone (MEK). Nuclear size was measured in histological sections either manually or by the Quantimet Image Analyser. Vehicle controls treated with 0.1% or 0.5% CO in acetone or MEK gave rise to epidermal hyperplasia with some nuclear enlargement; toluene without CO produced a similar response. When BP was applied in a vehicle capable of inducing hyperplasia, the nuclear enlargement produced was greater than that produced by either the vehicle control or BP in a nonirritant vehicle. The enhancement of the response to BP when BP was tested in the presence of a hyperplastic agent resulted in lower concentrations of BP being detectable. As the levels of BP detectable by nuclear enlargement under these conditions compared reasonably well with those detectable in long-term tests, this system might be useful as a short-term test for carcinogens. (19 refs)

79-5655 The Effects of Harman and Norharman on the Metabolism of Benzo(a)pyrene in Isolated Perfused Rat Lung and in Rat Lung Microsomes. (Eng) Vahakangas, K. (Dept. Pharmacology, Univ. Oulu, SF-90 220 Oulu 22, Finland); Pelkonen, O. *Biochem Pharmacol* 28(10): 1591-1596; 1979.

A comparative study was made of the effects of harman (HM) and norharman (NHM), nitrogen-containing pyrolysis products of amino acids present in cigarette smoke, on the metabolism of benzo(a)pyrene (BP) in Sprague-Dawley rat lung microsomes in vitro and in isolated perfused rat lung. In the microsomes, HM and NHM inhibited the metabolism of BP to dihydrodiols, phenols, and quinones at concentrations >0.05 mM. The formation of BP-7,8-dihydrodiol and BP-9,10-dihydrodiol was inhibited more than that of BP-4,5-dihydrodiol. No appreciable differences in inhibition were seen between microsomes from control or 3-methylcholanthrene-pretreated rats. In isolated perfused rat lung, 1 mM HM in the perfusion fluid inhibited the formation of all ethyl acetate-soluble metabolites of BP except for BP-9,10-dihydrodiol, and it inhibited the total covalent binding of BP metabolites to lung tissue macromolecules. At 0.03 mM, HM seemed to increase the formation of metabolites other than BP-7,8-dihydrodiol without changing the total covalent binding. These results suggest that at most concentrations, HM and NHM inhibit BP metabolism and covalent binding both in lung microsomes in vitro and in isolated perfused rat lung. (44 refs)

79-5656 Toxicity of Metabolic Benzo(a)pyrenediones to Cultured Cells and the Dependence upon Molecular Oxygen. (Eng) Lorentzen, R. J. (Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD 21205); Lesko, S. A.; McDonald, K.; Ts'o, P. O. *Cancer Res* 39(8): 3194-3198; 1979.

The toxicity of the three quinone metabolites of benzo(a)pyrene (BP), the 6,12-, 1,6-, and 3,6-dione, to cultures of Syrian hamster embryo cells was studied. At low concentrations (0.67 and 2.70 µg/ml), all three diones were toxic to the cells. The effect was dose-dependent, and it was greater at 48 hr than at 24 hr after treatment. BP 6,12-dione was slightly less effective than the other two diones. The reduction in cell number observed after treatment with these metabolites was the result of direct cell killing and inhibition of growth, since DNA synthesis was inhibited very early after treatment with BP 1,6-dione, when little cell death had occurred.

The rate of RNA synthesis was also inhibited by treatment of cells with BP 3,6-dione. These actions of the diones toward hamster cells could be eliminated or substantially reduced by the removal of oxygen from the growth medium and atmosphere in which the cells were incubated. In contrast, anaerobic conditions did not reduce the cytotoxicity observed with the alkylating agent ethyl methanesulfonate. These results support the hypothesis that BP diones, and other biologically active quinones, owe their activity to oxidation-reduction cycles involving quinone, hydroquinone, and molecular oxygen. The reactive reduced oxygen radicals and semi-quinone radicals formed during these cycles may be responsible for the observed cellular injury and inhibition of cellular processes. (30 refs)

- 79-5657 The Metabolism of Benzo(a)pyrene by Cytochrome P-450 in Transformable and Nontransformable C3H Mouse Fibroblasts. (Eng) Gehly, E. B. (Los Angeles County-Univ. Southern California Comprehensive Cancer Center, Los Angeles, CA 90033); Fahl, W. E.; Jefcoate, C. R.; Heidelberger, C. *J Biol Chem* 254(12): 5041-5048; 1979.

The microsomal metabolism of benzo(a)pyrene (BP) and its enhancement by inducers of aryl hydrocarbon hydroxylase (AHH) were studied in three C3H mouse fibroblast cell lines and in C3H mouse liver and lung. The cell lines examined included C3H/10T1/2CL8, a line that can be transformed by BP; CVP3SC6, a line that cannot be transformed by BP; and C3H/10T1/2CL16, a transformed cell line derived from 3-methylcholanthrene-treated C3H/10T1/2CL8 cells. Of four polycyclic hydrocarbons examined, benz(a)anthracene (BA) was found to be the most effective inducer of AHH activity, followed by BP and 7,12-dimethylbenz(a)anthracene; there was a complete absence of induction by 3-methylcholanthrene. The extent of induction in all three cell lines was dependent on the time after seeding that the inducer was added. The high-pressure liquid chromatographic profile of the BP metabolites was qualitatively identical for microsomes from all three cell lines, and it differed from the metabolism by liver and lung microsomes in that the cells did not produce detectable levels of BP-4,5-hydrodiol. The reduced CO cytochrome P-450 difference spectra of control and induced microsomes from all three cell lines showed a characteristic shift to shorter wavelengths after induction with BA. The specific activity of cytochrome P-450 in the cell microsomes closely paralleled the BP metabolizing activity, as measured in the AHH and high-pressure liquid chromatography assays. (34 refs)

- 79-5658 Differences in Benzo(a)pyrene Metabolic Profile in Rat and Mouse Ovary. (Eng) Mattison, D. R. (Pregnancy Res. Branch, Natl. Inst. Child Health and Human Development, NCI, NIH, Bethesda, MD 20205); West, D. M.; Menard, R. H. *Biochem Pharmacol* 28(13): 2101-2104; 1979.

Differences in polycyclic aromatic hydrocarbon (PAH) ovotoxicity and ovarian carcinogenicity between rats and mice suggest differences in toxic and nontoxic pathways of PAH metabolism in the rat and mouse ovary. Ovarian aryl hydrocarbon hydroxylase (AHH) activity was approx two times greater in B6 mice than in Sprague-Dawley rats, in both control and 3-methylcholanthrene (3-MC)-treated animals. No oocytes were destroyed in 3-MC-treated rats, but 87% were destroyed in treated mice. The gonads of the two species differed in their benzo(a)pyrene metabolic pathways. The lower production of the 7,8-diol by rat ovarian

monooxygenase is consistent with the greater resistance of the rat ovary to PAH ovotoxicity and ovarian carcinogenicity. (12 refs)

- 79-5659 Fluorescence Properties of a Benzo(a)pyrene 7,8-Dihydrodiol 9,10-Oxide-DNA Adduct. Conformation and Effects of Intermolecular DNA Interactions. (Eng) Prusik, T. (Squibb Inst. Medical Res., New Brunswick, NJ 08903); Geacintov, N. E. *Biochem Biophys Res Commun* 88(3): 782-790; 1979.

The pyrenelike fluorescence of the covalent benzo(a)pyrene (BP) diol-epoxide-DNA complex prepared by reacting the 7,8-dihydrodiol-9,10-oxide of BP (BPDE) with DNA in aqueous soln in vitro was investigated. This fluorescence was sensitive to molecular oxygen, to the concentration of native DNA, and to the ionic strength (KCl concentration) of the soln, but it was insensitive to the concentration of denatured DNA. These effects are related to the conformation of the pyrenelike chromophore of BPDE. Most of the fluorescence of a dilute soln of the DNA-bound BP derivative originated from binding sites in which the pyrene moiety was not intercalated between the DNA base pairs, but was located on the outside of the DNA double helix. (18 refs)

- 79-5660 Comparison of Benzo(a)pyrene and (-)-trans-7,8-Dihydroxy-7,8-dihydrobenzo(a)pyrene Metabolism in Human Blood Monocytes and Lymphocytes. (Eng) Okano, P. (Chemical and Physical Carcinogenesis Branch, NCI, NIH, Bethesda, MD 20205); Miller, H. N.; Robinson, R. C.; Gelboin, H. V. *Cancer Res* 39(8): 3184-3193; 1979.

Benzo(a)pyrene (BP) and (-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene [(-)-trans-7,8-diol] metabolism in human blood monocytes (MC's) and lymphocytes (LC's) was analyzed by high-pressure liquid chromatography, a procedure that required relatively low numbers of cells. The BP metabolite pattern included large amounts of the 7,8-diol, low or moderate levels of the 4,5-diol, and barely detectable levels of the 9,10-diol; at least three phenols, 3-, 7-, and 9-hydroxy-BP; and two major separable quinones, the BP-1,6- and 3,6-diones. BP metabolite patterns formed by benz(a)anthracene (BA)-induced MC's and LC's from the same individual showed that each cell type has characteristic differences in the relative ratios of BP metabolites formed. Relatively greater proportions of the 7,8-diol and 9-hydroxy-BP were synthesized by MC's, but LC's formed relatively higher levels of 3-hydroxy-BP and the BP quinones. Thus, it appears that MC's and LC's contain different patterns of cytochrome P-450 (CC P-450) mixed-function oxidases or metabolically related enzymes that are active in BP metabolism. The ratio of BP metabolites formed by BA-induced to that of control MC's and LC's was greater for the 7- and 9-hydroxy-BP's and smaller for 3-hydroxy-BP and the 7,8-diol in most samples examined. The total amounts of BP metabolites formed were quantitatively higher in BA-induced cells. These data suggest that BA induction was selective and favored the formation of certain forms of CC P-450 that change the metabolite patterns in induced cells. Both noninduced and BA-induced MC's and LC's metabolized the (-)-trans-7,8-diol further to highly mutagenic 7,8-diol-9,10-epoxides. Analysis of the ethyl acetate-extractable tetrols and triols demonstrated that the major diol-epoxide formed was *r*,7-*t*-8-dihydroxy-*t*-9,10-oxy-7,8,9,10-tetrahydro-BP. The results indicate that MC's and LC's exhibit different metabolite profiles, as do BA-induced and control cells. BA induction appears to favor BP over 7,8-diol metabolism, suggesting that the induction may lead to a greater ratio of detoxified to activated products relative to the ratio form-

ed in control cells. The results also show that the amount of 7,8-diol metabolism in BA-treated cells is either similar to or only slightly greater than that in control cells. This is in contrast to BP metabolism, which is stimulated 2- to 4-fold by BA. Thus, the form of CC P-450 metabolizing the 7,8-diol to diol-epoxides is relatively uninducible compared to those CC P-450 forms metabolizing BP. (46 refs)

- 79-5661 Effects of Smoking on Benzo(a)pyrene Metabolism by Human Placental Microsomes. (Eng) Vaught, J. B. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY 14263); Gurtoo, H. L.; Parker, N. B.; LeBoeuf, R.; Doctor, G. *Cancer Res* 39(8): 3177-3183; 1979.

Data demonstrating that the human placenta is capable of metabolizing benzo(a)pyrene (BP) to potentially carcinogenic metabolites are presented. Placentas were collected at term from a series of 21 women, 13 smokers and 8 nonsmokers. Microsomes were prepared and used in the following studies of BP metabolism: measurements of aryl hydrocarbon hydroxylase (AHH) and epoxide hydase levels, high-pressure liquid chromatographic (HPLC) analysis of BP metabolites, and assay of DNA-binding activation. DNA-binding adducts were further characterized by Sephadex LH-20 chromatography. AHH activity was much higher in smokers than in nonsmokers. Epoxide hydase activity with styrene oxide as the substrate was similar in the two groups. HPLC analysis showed much greater formation of dihydrodiols, quinones, and phenols by microsomes from smokers. The amount of benzo(a)pyrene-7,8-dihydrodiol was almost equal to the amount of phenols produced by the microsomes of the smokers. Sephadex LH-20 analysis of DNA binding resulted in only one major BP-DNA adduct when microsomes from smokers were used; this peak corresponded to benzo(a)pyrene 7,8-diol-9,10-oxide bound to DNA nucleoside(s). (54 refs)

- 79-5662 Dexamethasone-inhibited Aldosteroma (Variant of Primary Aldosteronism). (Rus) Zefirova, G. S. (Dept. Endocrinology, Central Inst. Advanced Training Physicians, Moscow, USSR); Gerasimenko, P. P.; Mirzaiants, G. G.; Ametov, A. S. *Ter Arkh* 51(6): 96-99; 1979.

A 38-yr-old woman with a history of hypertension presented with constant headache, asthenia, and periodic palpitation. Arteriography showed a shadow in the region of the left adrenal. The plasma aldosterone level was 800 picograms (pg)/ml, compared with 89.6 pg/ml in healthy controls. A diagnosis of dexamethasone-inhibited aldosteroma of the left adrenal was made. Administration of dexamethasone (4 mg/day, po, for 6 days) resulted in normalization of the blood pressure and the blood aldosterone level to 84 pg/ml. (13 refs)

- 79-5663 Metabolism of Prolactin in Mice with a High Incidence of Mammary Tumours: Evidence for Greater Conversion into a Non-immunoassayable Form. (Eng) Sinha, Y. N. (Lutcher Brown Center Diabetes and Endocrinology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Baxter, S. R. *J Endocrinol* 81(3): 299-314; 1979.

Experiments were conducted to determine whether prolactin (PL) is immunologically activated in the circulation of cancer-prone

mice. Monomeric mouse PL containing small amounts of 125 I-labeled PL was administered to adult female mice of a high (C3H/St) and low (C57BL/St) mammary tumor strain. Their endogenous PL had been suppressed with 2-bromo- α -ergocryptine. The chromatographic profile, on Sephadex G-100, of PL in the serum of mice injected with mouse PL was compared by direct measurement (radioactivity count) and by radioimmunoassay (RIA) at several intervals after injection. With both methods, the injected hormone was found in the serum in predominantly two molecular sizes, the so-called "big" and "little" forms. Although little PL in both strains constituted a constant 80% of the total PL level at most intervals by direct measurement, it comprised a comparatively smaller proportion by RIA. In addition, the RIA-determined little PL, after reaching max levels at 15 min, progressively decreased with time, the decrease being greater in the C3H/St than in the C57BL/St strain. Similar experiments with mouse growth hormone revealed no such discrepancies between the radioactivity counts and the RIA measurements. A fraction of big and little forms in the C3H/St strain failed to precipitate completely after the material had been incubated with an antiserum to mouse PL. These results demonstrate that the PL injected into mice is metabolized in serum into two nonimmunoreactive forms, one that elutes with the same elution volume on a Sephadex G-100 column as the monomer and the other that elutes as the big form. Furthermore, the loss of immunoreactivity of monomeric mouse PL is greater in the C3H/St strain than in the C57BL/St strain. Endogenous immunoreactive PL, on the other hand, was found mainly in the big form in the serum of C3H/St mice under basal conditions, whereas it was present only in the little form in C57BL/St mice, even though pituitary extracts of both strains contained mainly the little form. These results support the concept that monomeric PL in the systemic circulation of C3H/St mice is largely in a nonimmunoreactive form. (34 refs)

- 79-5664 Plasma Melatonin, Luteinizing Hormone, Follicle-stimulating Hormone, Prolactin, and Corticoids in Two Patients with Pinealoma. (Eng) Kennaway, D. J. (Dept. Obstetrics and Gynaecology, Queen Elizabeth Hosp., Adelaide, South Australia); McCulloch, G.; Matthews, C. D.; Seamark, R. F. *J Clin Endocrinol Metab* 49(1): 144-145; 1979.

Plasma melatonin was not detectable in two patients with pinealoma, but gonadotropin and cortisol levels were within the normal range. One patient, a 43-yr-old man, had low prolactin levels and the other patient, a prepubertal boy, had elevated levels. The clinical value of melatonin as a potential marker for pineal tumors is questionable. (5 refs)

- 79-5665 Mammary Tumour Incidence in Relation to the Pattern of Oestrous Cycles in Mice. (Eng) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Yanai, R.; Taniguchi, H.; Hayashi, S. *Horm Res* 10(2/3): 123-129; 1979.

The estrous cycles of SHN and SLN mice, two new strains that exhibit a high and a low mammary tumor incidence, respectively, were compared. These mice originated from the same stock of Swiss albino mice. At the age of 3-4 mo, SHN mice showed much longer cycles with continual diestrous periods than SLN mice. The av lengths of the cycles and diestrous periods were, respectively, 8.3 and 6.0 days in SHN mice and 4.6 and 2.5 days in SLN mice. Furthermore, a distinct alteration in cycle pattern from an SHN to an SLN type was associated with a complete reduction in mam-

mary tumor incidence in highly inbred C3H/He female mice maintained by brother x sister mating with no selection for mammary tumorigenesis. The relation between the pattern of estrous cycles and mammary tumorigenesis is considered from the viewpoint of the endogenous hormonal milieu and the responsiveness of target organs. (16 refs)

- 79-5666 Virilizing Syndrome Associated with an Adrenal Cortical Adenoma Secreting Predominantly Testosterone. (Eng) Schteingart, D. E. (Univ. Hosp., Room S3450, Ann Arbor, MI 48109); Woodbury, M. C.; Tsao, H. S.; McKenzie, A. K. *Am J Med* 67(1): 140-146; 1979.

A 22-yr-old woman with virilization and mild Cushing's syndrome associated with a testosterone (TS)-secreting left adrenal adenoma is described. The patient had a high serum TS level, a mildly elevated urinary 17-ketosteroid level, and a normal plasma cortisol level. The basal level of cortisol secretion was normal but with evidence of autonomy. The tumor was capable of secreting TS, cortisol, dehydroepiandrosterone (DHEA), and 17 β -estradiol (E2), but the capacity was greatest for TS, DHEA, and E2. (29 refs)

- 79-5667 Teratogenesis and Carcinogenesis in Rat Offspring After Transplacental and Transmammary Exposure to Diethylstilbestrol. (Eng) Vorherr, H. (Dept. Obstetrics-Gynecology, Univ. New Mexico, Sch. Medicine, Albuquerque, NM 87131); Messer, R. H.; Vorherr, U. F.; Jordan, S. W.; Kornfeld, M. *Biochem Pharmacol* 28(12): 1865-1877; 1979.

Female offspring of pregnant and/or lactating rats that received diethylstilbestrol (DES: ≥ 0.05 mg/kg/day, sc) had abnormal development of the urogenital sinus. Vaginal adenosis, endometrial squamous metaplasia, and genital malignancy were encountered in 20%-40% of these offspring. In exposed male offspring, hypospadias, phallic hypoplasia, inhibition of growth and descent of testes, and abnormalities of Wolffian derivatives were observed. (53 refs)

- 79-5668 Glandular Dysplasia in Diethylstilbestrol-associated Vaginal Adenosis. A Case Report and Review of the Literature. (Eng) Antonioli, D. A. (Dept. Pathology, Beth Israel Hosp., 330 Brookline Ave., Boston, MA 02215); Rosen, S.; Burke, L.; Donahue, V. *Am J Clin Pathol* 71(6): 715-721; 1979.

In a 21-yr-old nulliparous woman with diethylstilbestrol (DES)-associated vaginal adenosis, dysplastic glands were identified and examined by light and electron microscopy. Transitions between normal and dysplastic glands were documented in subserial sections. These alterations may characterize an intermediate phase in the development of clear-cell adenocarcinoma of the vagina. Documented glandular dysplasia in adenosis is rare: in an evaluation of 550 DES-exposed women, only two cases (including the present one) were found. (15 refs)

- 79-5669 Adenosis-like Lesions and Other Cervicovaginal Abnormalities in Mice Treated Perinatally with Estrogen. (Eng) Plapinger, L. (Population Council, Rockefeller Univ., 1230

York Ave., New York, NY 10021); Bern, H. A. *J Natl Cancer Inst* 63(2): 507-518; 1979.

The effects of perinatal estrogen treatment on cervicovaginal histogenesis were determined in female mice from three inbred strains (BALB/cCrgl, C3H/Crgl, and C57BL/Crgl) and one noninbred stock [RU:NCS (RU)]. The mice were treated with estradiol benzoate (EB), diethylstilbestrol (DES), or sesame oil and killed on postnatal days 30-36. A combined prenatal and neonatal regime of EB injections resulted in the abnormal presence of columnar epithelium in the vaginal fornices of some of the mice from each strain or stock. The same epithelial abnormalities were also present in the vaginal fornices of 30-day-old RU:NCS(RU) mice that had been treated only neonatally with EB or DES. The incidence of these lesions was 40%-67% in mice treated prenatally and neonatally with EB, 68% in the neonatal EB treatment group, and 100% in the neonatal DES treatment group. The columnar cells were arranged either as single layers in areas of the fornical lining epithelium or as glandlike or cystic structures in the subepithelial stroma. No cells of this type were detected in any of the samples from sesame oil-inoculated control mice. No comparable epithelial lesions were detected in the common cervical canal of the perinatally estrogen-treated animals, but this treatment consistently resulted in gross structural abnormalities at this site. (25 refs)

- 79-5670 Long-Term Effects of Neonatal Estrogen Treatment on Mitogen Responsiveness of Mouse Spleen Lymphocytes. (Eng) Kalland, T. (Inst. Anatomy, Arstadvei 19, 5000 Bergen, Norway); Strand, O.; Forsberg, J. G. *J Natl Cancer Inst* 63(2): 413-421; 1979.

The effect of neonatal estrogen treatment on the in vitro responsiveness of spleen lymphocytes from adult mice to T- and B-cell mitogens was studied. Neonatal female NMRI mice were given sc injections of olive oil (controls) or daily doses of corticosterone (10 μ g), 17 β -estradiol (10 μ g), or diethylstilbestrol (DES: 0.01, 0.1, 1, or 5 μ g) for the first 5 days after birth. The 5- μ g dose of DES resulted in a persistently reduced in vitro mitogen response of spleen lymphocytes from 6-, 10-, and 18-wk-old and 17-mo-old females to concanavalin A or bacterial lipopolysaccharide. DES injections from day 6 through day 10 did not influence the later mitogen response. Treatment of ovariectomized 10-wk-old females with 5 μ g DES for 5 days resulted in a statistically nonsignificant reduced mitogen response 24 hr after the last injection. Four weeks later, the mitogen response was the same in experimental and control females. Different possible mechanisms for the persistent effect on the mitogen response are discussed. Neonatal DES treatment not only resulted in persistent changes in the cervicovaginal epithelium and in the hypothalamic-pituitary gland control system, but also in the spleen lymphocyte mitogen response. The altered mitogen response should be a stimulus for a detailed analysis of the immune system in women exposed to DES during fetal life, some of whom develop clear cell adenocarcinoma of the uterine cervix and vagina later in life. (48 refs)

- 79-5671 Association of Diethylstilbestrol Exposure In Utero with Cryptorchidism, Testicular Hypoplasia and Semen Abnormalities. (Eng) Gill, W. B. (Dept. Surgery (Urology), Univ. Chicago, Chicago, IL); Schumacher, G. F.; Bibbo, M.; Straus, F. H.; Schoenberg, H. W. *J Urol* 122(1): 36-39; 1979.

The occurrence of genital tract abnormalities among 308 men exposed to diethylstilbestrol and 307 men exposed to a placebo 25 yr

previously (in utero) was studied. The incidences of epididymal cysts and testicular hypoplasia were significantly greater among the DES-exposed men (20.8% and 8.4% for the two conditions, respectively) than among the placebo controls (4.9% and 1.9%, respectively). Cytological examination of the fluid aspirated from the epididymal masses of nine DES-exposed men showed only epithelial cells and amorphous precipitates without any material suggestive of malignancy. Similarly, the urine and prostatic fluid of DES-exposed and control men were negative for tumor cells. Of the 26 DES-exposed men with testicular hypoplasia, 65% had a history of cryptorchidism, compared with only 1/6 of the controls with testicular hypoplasia. The DES-exposed and control subjects did not differ significantly with respect to levels of circulating blood hormones. The av sperm density was somewhat decreased in the DES-exposed men compared with controls, and the av Eliasson score (sperm count, sperm motility, motility grade, and sperm morphology) was significantly higher in the DES-exposed group (4.9) than in the controls (2.5). (15 refs)

79-5672 Effects of Oral Contraceptives and Pregnancy on Melanomas (Letter to Editor). (Eng) Lerner, A. B. (Yale Univ. Sch. Medicine, New Haven, CT 06510); Nordlund, J. J.; Kirkwood, J. M. *N Engl J Med* 301(1): 47; 1979.

Three cases are reported of female patients in whom the development or metastasis of a melanoma was associated with estrogen or progesterone administration, or with pregnancy. One patient had a superficial spreading melanoma removed at the age of 13 yr and had no evidence of metastasis until 8 mo after she began taking an anovulatory drug at the age of 19 yr. Another patient developed melanoma in a nevus of Ota 2 yr after commencing oral contraceptive use. The third patient developed ulceration and bleeding of a nevus with subsequent metastasis in association with pregnancy. (4 refs)

79-5673 Carcinogenic Activity of 2-Aminoacetophenone in Syrian Hamsters. (Rus) Khar'kovskaia, N. A. (Dept. Lab. Animals, Cancer Res. Center, Moscow, USSR). *Vopr Onkol* 25(6): 81-84; 1979.

The carcinogenicity of 2-aminoacetophenone (2-AAP: 10 mg sc 2x/wk for 10 wk) was studied in Syrian hamsters. 2-AAP increased the incidence of tumors: 23/39 treated hamsters developed tumors,

compared with 33/95 controls. Of 23 tumor-bearing treated hamsters, 18 had tumors of the endocrine system (14/18 were tumors of the adrenal cortex), but only 19/33 tumor-bearing control hamsters had spontaneous tumors of the endocrine system (16/19 were tumors of the adrenal cortex). 2-AAP also induced an adenoma in the medullary layer of the adrenal, granulocellular ovarian tumor, a seminoma, a squamous cell lung carcinoma, and a urinary bladder carcinoma. (4 refs)

79-5674 Gossypol-Proposed Contraceptive for Men Passes the Ames Test (Letter to Editor). (Eng) de Peyster, A. (Univ. California Sch. Public Health, Berkeley, CA 94720); Wang, Y. Y. *N Engl J Med* 301(5): 275-276; 1979.

The results of two separate mutagenicity assays of gossypol using the Ames salmonella-microsome test indicated that the new contraceptive is not mutagenic to the five standard tester strains of *S. typhimurium*, either with or without inclusion of a rat liver metabolic-enzyme fraction (S9). (4 refs)

See also:

*(Rev.): 79-5401, 79-5402, 79-5403, 79-5404, 79-5405, 79-5406, 79-5407, 79-5408, 79-5409, 79-5410, 79-5411, 79-5412, 79-5413, 79-5414, 79-5415, 79-5416, 79-5417, 79-5418, 79-5419, 79-5420, 79-5421, 79-5422, 79-5423, 79-5424, 79-5425, 79-5426, 79-5427, 79-5428, 79-5429, 79-5430, 79-5431, 79-5432, 79-5433, 79-5434, 79-5435, 79-5436, 79-5437, 79-5438, 79-5439, 79-5440, 79-5441, 79-5442, 79-5443, 79-5445, 79-5447, 79-5467, 79-5471, 79-5482, 79-5494, 79-5495, 79-5499, 79-5502, 79-5503, 79-5505, 79-5509, 79-5510.

*(Phys.): 79-5675, 79-5685, 79-5688, 79-5692.

*(Viral): 79-5714, 79-5727, 79-5728, 79-5734, 79-5746, 79-5753, 79-5759, 79-5797.

*(Immun.): 79-5832, 79-5835, 79-5843.

*(Path.): 79-5863.

*(Epid.-Biom.): 79-5926, 79-5929, 79-5930, 79-5932, 79-5933, 79-5935, 79-5938, 79-5939, 79-5940, 79-5941, 79-5942, 79-5949, 79-5950, 79-5957, 79-5960, 79-5963, 79-5972, 79-5973, 79-5975.

PHYSICAL CARCINOGENESIS

79-5675 In Vitro Comparison of Normal and Trisomic Cell Sensitivity to Physical and Chemical Mutagens. (Eng) Kucerova, M. (Genetics Lab., Inst. Hygiene and Epidemiology, Srobarova 48, 10042 Prague 10, Czechoslovakia); Polikova, Z. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 185-190; 1978.

The in vitro sensitivity of normal and trisomic cells to radiation was compared, along with the sensitivity of these cells to mitomycin C. Lymphocytes from four healthy male donors and from four males with Down's syndrome were irradiated with 100, 200, 300 or 400 rads of x-rays or exposed to 10^{-4} to 10^{-6} mg/ml mitomycin C. The numbers and types of chromosome aberrations were analyzed by the conventional technique, and the yield of sister-chromatid exchanges (SCE's) was scored by the fluorescence plus Giemsa technique. As expected, the radiosensitivity of trisomic cells, measured by the number of chromosome aberrations, was higher than that of normal cells. The number of SCE's in both types of cells exposed to 100 rads was not significantly changed in comparison with controls. The sensitivity of trisomic and normal cells to mitomycin C appeared to be similar. The frequency of aberrations and SCE's in both types of cells was dependent on the concentration of the drug. (7 refs)

79-5676 Metabolism of Nucleic Acids in Radiosensitive Tissues of Rats after Single Administration of Tritium Hydroxide. (Rus) Shorokhova, V. B. (No affiliation given); Revina, V. S.; Turdakova, V. A.; Mushkacheva, G. S. *Radiobiologiya* 19(3): 323-329; 1979.

The immediate and long-term effects of a single po dose of tritium hydroxide (T-OH: 0.6 mCi/g) were studied in male Wistar rats. Animals were sacrificed at different times after exposure, and the rate of synthesis of nucleic acids in the bone marrow, spleen, and thymus was determined. T-OH decreased the life-span of the rats by 40% (419 days, compared with 699 days in controls) and increased the incidence of tumors: 11.8% had connective tissue tumors (vs 1.2% in controls), 8.9% had mammary gland tumors (vs 2.3%), 10.8% had lung tumors (vs 3.4%), 1.9% had kidney tumors (vs 0%), 3.9% had bone tumors (vs 0%), and 2.9% had leukemias (vs 3.4%). The duration of survival of the tumor-bearing rats was 454 days, compared with 606 days for tumor-bearing rats that were not treated with T-OH. Analysis of the level and rate of nucleic acid synthesis revealed that there was a marked decrease in the concentration of DNA in radiosensitive tissues: on days 3-7 of exposure, there was a 30%-40% decrease of the DNA level in the bone marrow and thymus and a 60% decrease in the spleen. Starting on day 14 of exposure, DNA levels showed a tendency toward normalization, but later there was a second 25%-30% decrease of DNA levels in the bone marrow and spleen (12 mo after exposure) and an approx 50% decrease in the thymus (6 and 12 mo after exposure). (12 refs)

79-5677 Dynamics of Changes in Connective Tissue of Rats During Ethacryl (AKP-15)-induced Tumorigenesis.

(Rus) Eliseev, V. V. (Lab. Chemical Carcinogens, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR). *Vopr Onkol* 25(6): 65-69; 1979.

The effect of the implantation of plastic Ethacryl (AKP-15) plates was studied in random-bred albino rats. Plates measuring 20 x 20 x 1 mm were implanted sc, and the animals were followed for 1-16 mo. A connective tissue capsule that was composed of three layers was formed by the end of the first month of implantation. Proliferative activity began to subside 3 mo after implantation, but 6 mo after implantation, some capsules contained foci of diffuse proliferation in the internal layer. These foci consisted of immature fibroblasts without signs of cellular atypia. Foci of atypical cells were first detected by 10-11 mo after implantation. Progressive replacement of the capsule tissue was followed by the formation of a tumor nodule. (10 refs)

79-5678 Competitive Radiation-induced Carcinogenesis: An Analysis of Data from Beagle Dogs Exposed to ^{226}Ra and ^{90}Sr . (Eng) Momeni, M. H. (Div. Environmental Impact Studies, Argonne Natl. Lab., Argonne, IL 60439). *Health Phys* 36(3): 295-310; 1979.

The incidence of radiation-induced primary bone sarcoma and myeloproliferative disease was studied as a function of dose rate and time in 776 beagles. The dogs were fed diets containing $^{90}\text{SrCl}_2$ in equilibrium with ^{90}Y from midgestation to 1.5 yr of age or they were given eight iv injections of $^{226}\text{RaCl}_2$ (one injection every 2 wk for 4 mo) starting at 14 mo of age. Analysis of the incidence of each disease in the beagles showed a normal probability density function with respect to time. Median incidence time and standard deviation from the mean of distribution were calculated for primary osteosarcoma at each level of administered radioactivity. The median incidence age (T) for mortality from primary osteosarcoma increased from 4.1 yr, 2.6 yr after the final radium injection, for beagles injected (A_0) with 83.6 μCi ^{226}Ra , to 11.5 yr for beagles given $A_0 = 3.14 \mu\text{Ci}$ ^{226}Ra . For beagles that ingested a daily diet containing $^{90}\text{Sr} + ^{90}\text{Y}$, from T increased 2.8 yr at 36 μCi ^{90}Sr /day to 12.6 yr at 4 μCi ^{90}Sr /day. Tumor yield was calculated assuming that the causes of death from competing diseases were mutually exclusive with respect to individual diseases. Incidence and cumulative incidence for each of the diseases were calculated as a function of time and max dose rate. These analyses were extended to beagles administered ^{226}Ra by a single injection or ^{90}Sr by injection and inhalation. Extrapolation of the observed dose effects to lower levels of administered radioactivity (comparable to max permissible body burden) is discussed within the frame of a competitive mortality from factors unrelated to radiation. (48 refs)

79-5679 Cytogenetic Investigation of People in Finland Using Household Water with High Natural Radioactivity. (Eng) Stenstrand, K. (Inst. Radiation Protection, Box 268, SE-00101 Helsinki 10, Finland); Annanmaki, M.; Rytomaa, T. *Health Phys* 36(3): 441-444; 1979.

Peripheral lymphocytes obtained from 18 individuals (aged 13-74

yr) living in five different dwellings where the household water has high natural radioactivity (^{222}Rn) were examined for frequency of chromosome aberrations. Nine men (aged 23-45 yr) served as controls. Slides prepared from 48-hr harvests were scored for the prevalence of dicentrics, centric rings, and acentrics. A total of 6,752 cells from the exposed group were analyzed, and 42 showed chromosome aberrations (18 dicentrics, 1 centric ring, 34 acentrics); 14/4,520 cells from the control group showed chromosome aberrations (1 dicentric, 1 centric ring, 12 acentrics). The total number of chromosome aberrations and the frequency of breaks resulting in dicentrics were significantly higher ($P < 0.001$) in the exposed group. (15 refs)

- 79-5680** An Investigation of UV-induced Chromosome Changes in Relation to Lethality in Normal and UV-sensitive Human Cells. (Eng) Scott, D. (Paterson Labs., Christie Hosp., Manchester M20 9BX, England); Marshall, R. R. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977.* Medical Research Council (Edinburgh, Scotland): 355 pp.; 129-141; 1978.

The role of chromosome (CS) damage in UV-induced cell lethality and other mechanisms of cell death were investigated, and cytogenetic studies were carried out in normal and UV-sensitive human cells. CS structural aberrations, chiefly chromatid deletions and a few exchanges, were more frequent in xeroderma pigmentosum XP25RO cells than in normal 1BR cells following UV irradiation [0.5 or 1.0 joule (J/m^2)]. The only effect of the lower UV dose on cell-cycle times was to increase the S phase in XP25RO cells from 7.75 to 10.25 hr. A comparison of the labeled mitosis curves with those for metaphase aberration frequencies after the lower UV dose indicated that the aberrations were mainly in first division 1BR cells and in second- and third-division XP25RO cells. Only aberrations that affect both daughter cells and that arise during the first division can have a significant effect on colony-forming ability; hence, the frequency of these aberrations (3.3%) in UV-irradiated XP25RO cells is too small to account for the degree of cell killing (87%). Moreover, interphase death (occurring in 20% of postirradiation XP25RO cells) in combination with a 4% CS aberration frequency in both daughter cells from cells (80%) that do undergo their first mitosis can account for only about 23% of cell death. The death of UV-irradiated XP25RO cells, occurs mainly after their second division. Only occasional anaphase fragments and no CS bridges or multipolar divisions were seen in 1BR or XP25RO cells exposed to 0.5 J/m^2 UV light. Metaphase CS structural aberrations were not increased above control levels in 1BR cells or 11961 cells (from a UV-sensitive individual without detectable DNA repair defects) exposed to 1.5 J/m^2 UV light, although this dose killed approx 20% and 90% of the cells, respectively. A few bridges and anaphase fragments but virtually no multipolar mitoses were observed in these cells, either in control or irradiated populations. UV radiation did not markedly increase the frequency of sister chromatid exchanges (SCE's) in 11961 cells, and the spontaneous frequency of SCE's in these cells was a little higher than that in 1BR cells. Hence, cell death due to UV irradiation cannot be attributed to an increased frequency of SCE's. It is concluded that conventional CS structural aberrations play little or no role in UV-induced cell lethality. (25 refs)

- 79-5681** A Cytogenetic Study of Hiroshima Atomic-Bomb Survivors. (Eng) Sofuni, T. (Cytogenetics Section, Dept. Clinical Labs., Radiation Effects Res. Foundation, 5-2 Hi-

jiyama Park, Hiroshima 730, Japan); Shimba, H.; Ohtaki, K.; Awa, A. A. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977.* Medical Research Council (Edinburgh, Scotland): 355 pp.; 108-114; 1978.

A total of 896 metaphases from 2-day cultures of peripheral blood lymphocytes from 23 heavily exposed Hiroshima A-bomb survivors were examined first after conventional staining, then reexamined after trypsin G-band staining. The frequencies of cells with radiation-induced chromosome aberrations, mainly of the symmetric type, were compared for the two methods. Abnormal karyotypes were detected in 348 metaphases by either one or both methods. Of these aberrant cells, 293 were found to have chromosome aberrations by the conventional stain. There were 55 metaphases in which abnormalities were detected only by G-banding. Six cells were identified as abnormal by the ordinary stain but as normal by G-banding; four of these were misidentified in the ordinary preparation due to the presence of partially distorted chromosomes. Further G-banding analysis identified various exchanges, including several types of insertions and paracentric inversions, which could not be detected by the conventional technique. (10 refs)

- 79-5682** The Influence of DTPA on the Metabolism of Inhaled $^{239}\text{PuF}_4$ in Beagles. (Eng) McDonald, K. E. (Biology Dept., Pacific Northwest Lab., Richland, WA 99352); Dilley, J. V.; Sanders, C. L.; Mahaffey, J. A. *Health Phys* 36(5): 632-635; 1979.

The metabolism and translocation of ^{239}Pu inhaled as a fluoride and the effectiveness of dicalcium trisodium diethylenetriamine-pentaacetic acid (DTPA) therapy for the removal of inhaled $^{239}\text{PuF}_4$ were investigated in beagle dogs. Three dogs were exposed to the dry aerosol of $^{239}\text{PuF}_4$ only, while 2 hr after exposure, three dogs were injected ip with 0.5 g DTPA diluted to 10 ml with normal saline. DTPA injections were given on days 1, 4, 7, 11, 16, 18, 23, 37, 44, 51, and 58. The whole-body burden was monitored by whole body counting. On day 85 postexposure the dogs were killed, and complete necropsies were performed. The initial body burden for all six dogs averaged $9.5 \pm 6.1 \mu\text{Ci}$, and the initial alveolar deposition for all dogs averaged $1.3 \pm 0.7 \mu\text{Ci}$. The only significant difference in the $^{239}\text{PuF}_4$ content in organs was obtained in the liver: dogs treated with DTPA averaged 0.0048% while those not treated averaged 0.1%. This difference was considered insignificant since the amount of ^{239}Pu in the liver was small in both groups. One dog, for unknown reasons, excreted a great deal more plutonium than the other five dogs. When this dog was excluded, plutonium urinary excretion was higher in treated animals, but this increase was not statistically significant. It was concluded that $^{239}\text{PuF}_4$ in the lung is unresponsive to DTPA chelation therapy. (3 refs)

- 79-5683** Estimation of Long-Term Biological Elimination of Insoluble ^{192}Ir from the Human Lung. (Eng) Cool, D. A. (Radiation Biology and Biophysics, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY 14642); Cool, W. S.; Brodsky, A.; Eadie, G. G. *Health Phys* 36(5): 629-632; 1979.

An opportunity to study the long-term retention/elimination pattern of insoluble ^{192}Ir in the human lung arose from an inhalation accident involving two subjects in which approx 2 Ci escaped undetected from a hot cell. Initial in vivo measurements taken ap-

prox 14 hr postexposure (PE) indicated a deposition of about 412 and 278 μCi in the lungs of Subjects 1 and 2, respectively. The second measurement at 33 hr PE showed that 53.6 and 16.3 μCi of the material remained in the lungs, respectively; the lost activity was accounted for by the activity measured in the first day's fecal sample. Between days 4 and 6 PE, the remaining lung burden decreased approx 6.6%/day for Subject 1 and 2.5%/day for Subject 2, and weekly fecal samples collected over the 2-yr study period indicated a total elimination rate consistent with a biological half-life of $>1,000$ days. Urine samples collected during this period had very low activity, indicating that elimination did not proceed through the circulatory system. Lung scans from 2 days to 6 mo PE showed patterns of relatively uniform deposition and retention of particulates throughout the pulmonary regions of both subjects. Starting 13 days PE, a standard chair whole-body counting technique with two scintillation detectors (1 adjacent to the chest and 1 approx 1 m from the subject) was used to measure radionuclide activity in the subjects. Regression analysis gave biological half-life values of 2,220 and 2,870 days with the detector adjacent to the chest and 982 and 714 days with the detector at a 1-m distance. The difference between the effective half-lives became increasingly significant over the 2-yr test period and could not be explained by statistical variation at the 95% confidence level. One possible explanation for the difference is the biological translocation of the material over time. (15 refs)

79-5684 Nasal Carcinomas in Beagles after Inhalation of Relatively Soluble Forms of Beta-emitting Radionuclides. (Eng) Benjamin, S. A. (Collaborative Radiological Health Lab., Coll. Veterinary Medicine and Biomedical Sciences, Colorado State Univ., Fort Collins, CO 80523); Boecker, B. B.; Cuddihy, R. G.; McClellan, R. O. *J Natl Cancer Inst* 63(1): 133-139; 1979.

At 12-14 mo of age, beagles were exposed by inhalation to relatively soluble forms of single beta-emitting radionuclides, and they are being observed over their life-spans to determine biologic hazards associated with nuclear power production. The dogs were exposed to graded activity levels of $^{91}\text{YCl}_3$, $^{144}\text{CeCl}_3$, or $^{90}\text{SrCl}_2$. With $^{91}\text{YCl}_3$ and $^{144}\text{CeCl}_3$, a significant radiation dose was delivered to the respiratory tract, liver, and skeleton. With $^{90}\text{SrCl}_2$, the dose was almost totally to the skeleton. Squamous cell carcinomas associated with the nasal cavity were the most frequently observed neoplasms in the $^{91}\text{YCl}_3$ study and one of the most frequent in the $^{144}\text{CeCl}_3$ study, whereas few squamous cell carcinomas were seen with $^{90}\text{SrCl}_2$. One nasal cavity hemangiosarcoma was also seen with ^{144}Ce . The incidence of nasal carcinomas may be related to higher relative concentrations of the radionuclides ^{91}Y and ^{144}Ce in the nasal turbinates. This relatively high risk of nasal cavity neoplasms suggests that standards for human exposure to these radionuclides should include a consideration of nasal cavity epithelium as a major target tissue. (29 refs)

79-5685 Effects of Low-Level X-Radiation on 7,12-Dimethylbenz(a)anthracene-induced Lingual Tumors in Syrian Golden Hamsters. (Eng) Lurie, A. G. (Dept. Oral Diagnosis-Oral Radiology, Univ. Connecticut Health Center, Sch. Dental Medicine, Farmington, CT 06032); Cutler, L. S. *J Natl Cancer Inst* 63(1): 147-152; 1979.

The effects of repeated low-level x-radiation of the head and neck on lingual tumor induction by 7,12-dimethylbenz(a)anthracene (DMBA) were studied in Syrian Golden hamsters. Animals received

either topical application of 0.5% DMBA in acetone on the lateral middle third of the tongue 3x/wk for 15 consecutive wk, 20-R x-radiation exposures to the head and neck once a week for 15 wk, or concurrent radiation and DMBA treatments for 15 wk. Animals were examined visually at regular intervals, and all were killed 35 wk after the start of treatments. All tissues were then examined histopathologically. Animals receiving radiation alone had no detectable changes. Animals receiving DMBA + radiation had an excess of papillomas compared with animals receiving only DMBA (35% vs 15%). In addition, an excess of nonlingual oral tumors (lip, gingiva, and floor of mouth) was found in DMBA + radiation-treated animals vs DMBA-treated animals. These results suggest that repeated, localized, low-level x-radiation enhances chemical tumorigenesis in a variety of oral tissues of Syrian golden hamsters. (14 refs)

79-5686 Plutonium in the Tissues of Foetal, Neonatal and Suckling Mice after Pu-Administration to Their Dams. (Eng) Green, D. (Medical Res. Council Radiobiology Unit, Harwell, Didcot, Oxfordshire, England); Howells, G. R.; Watts, R. H. *Int J Radiat Biol* 35(5): 417-432; 1979.

The uptake of plutonium-239 by the mouse fetus, membranes, and placenta during gestation and its distribution in the 1-day-old neonate and the 18-day-old suckling were determined. Twelve-wk-old female (C3H x 101)F₁ mice were injected iv with an ultrafiltered soln of ^{239}Pu in 1% trisodium citrate, and mated to uninjected PCT males. The Pu content was examined radiochemically and autoradiographically in the placenta and fetuses on gestation days 12 and 18, in neonates during the 24 hr after birth, and in sucklings 18 days postnatally. The distribution of Pu in most tissues of the late fetus and the suckling was similar to that in adult mice. However, on gestation days 12 and 18, the concentration in the yolk-sac splanchnopleura was much higher than that in any other fetal tissue. The amount of ^{239}Pu in 18-day-old sucklings was between two and seven times as great as that in 1-day-old neonates because of the ingestion of milk from lactating dams. In the first litter following administration of the radionuclide to the dam, about 0.02% of the Pu injected was transferred to each offspring by the time of birth and a further 0.08% was transferred by the time of weaning. (18 refs)

79-5687 Ionizing Radiation Perturbs the Switch-on of Transcriptase in a Model Transcription Complex In Vitro. (Eng) Borsa, J. (Medical Biophysics Branch, Whiteshell Nuclear Res. Establishment, Atomic Energy Canada Ltd., Pinawa, Manitoba ROE 1LO, Canada); Sargent, M. D.; Lievaart, P. A. *Int J Radiat Biol* 35(5): 459-472; 1979.

A model in vitro transcription complex derived from reovirus type 3 was used to study the effect of ionizing radiation on cellular functions. The model complex, the intermediate subviral particle (ISVP), is converted from a blocked [inactive transcriptase (TS)] to an unblocked (active TS) form by an endogenous switch mechanism triggered by the intracellular (physiological) K⁺ concentration. Intact virions, ISVP's and virus core particles were irradiated in a cobalt-60 gamma-ray chamber at 7.9 krad/min. Intact reovirions and ISVP's contain blocked endogenous TS; virus core particles contain unblocked endogenous TS. Irradiating intact virions failed to unblock TS activity; irradiating core particles inactivated TS activity with single-hit kinetics; and irradiating ISVP's unblocked TS activity in a dose-dependent manner: TS activity at first increased, passed through a max, and then decreased

to background levels. A synergistic interaction was demonstrated between ionizing radiation and K^+ concentration in effecting TS switch-on: (1) increasing doses of radiation lowered, in a dose-dependent fashion, the concentration of K^+ required to trigger switch-on; (2) radiation could not effect switch-on in the absence of K^+ , but increasing concentrations of K^+ increased the effectiveness of a given radiation dose to trigger switch-on. These results suggest that ionizing radiation stably alters the ISVP in some way, changing its response to K^+ stimulation. When the response of control and irradiated ISVPs to K^+ stimulation was compared in the presence of various perturbations (bentonite, chymotrypsin, Hg^{2+} , varying temperature), the two species were identical, indicating that the unblocking mechanism is identical in the two types of ISVP. The size distributions of product RNA synthesized by irradiated and unirradiated ISVP's were very similar, indicating that the K^+ -radiation-induced readout produces functional messenger RNA and that the decline in TS activity at high radiation doses is not due to premature termination of transcription. Biophysical characterization of irradiated and control ISVP's ruled out a loss of particle components or a change in their packing arrangement. However, in irradiated particles, the major polypeptide band δ , is split into two species upon electrophoresis. This change may account for the TS-unblocking effect of radiation on ISVP's. (54 refs)

- 79-5688 Photoreactivation of Ionizing-Radiation-induced Damage in *E. coli*. Influence of Chemical and Physical Factors. (Eng) Redpath, J. L. (Div. Radiation Oncology, Dept. Radiobiological Sciences, Univ. California, Irvine, CA 92717); Zabilansky, E. *Int J Radiat Biol* 35(5): 473-476; 1979.

Evidence is presented to support the hypothesis that photoreactivatable damage to DNA is the same whether produced by UV or ionizing radiation. *Escherichia coli* strains Bs-1 (*uvrBexrA*) and AB2480 (*uvrArecA*) were used; late log-phase cells were diluted to a concentration of 10^6 cells/ml, irradiated in the dark, and exposed to low-intensity room light or a high-intensity light source. Because caffeine inhibits the photoreactivation (PR) of UV-induced damage by competing with the PR enzyme for its substrate, the effect of caffeine on PR in Bs-1 cells treated with ionizing radiation was examined. Caffeine reduced the rate of PR in low-intensity light by a factor of about 4. Thus, the effect of caffeine on PR is similar whether the damage is induced by UV or by ionizing radiation. The effect of the radioprotective agent dithiothreitol (DTT) on the amount of photoreactivatable damage following a dose of ionizing radiation was examined. The presence of DTT during irradiation of Bs-1 or AB2480 cells did not reduce the amount of damage, indicating that the mechanism of irradiation damage is not likely to be mediated by free radicals. This finding favors a mechanism involving the production of an excited state in the target. The extent of PR in both Bs-1 and AB 2480 cells was measured following various doses of x-rays. The energy of the damage-inducing x-radiation influenced the extent of repair, with little or no PR being observed below a certain dose. The mechanism of this dependence is currently under investigation. (7 refs)

- 79-5689 Radiation Risk and Gonad Exposure from Diagnostic X-rays. (Ger) Vogel, H. (Abt. Röntgendiagnostik, Radiologischen Univ.-Klinik im Klinikum Hamburg-Eppendorf, Martinistrasse 52, D-2000 Hamburg 20, W. Germany). *Munch Med Wochenschr* 121(28): 943-946; 1979.

The risks of malignancy or mutation induction from low levels of radiation were calculated based on data from the International Council on Radiation Protection (ICRP: Report 26) and the author's own measurements. Radiation of one million persons with 1 rem (radiation-equivalent-man) is estimated to lead to 100 additional malformations caused by mutations in the next two generations; the spontaneous rate is 3%. Risks from special diagnostic tests were also calculated: one malformed child is to be expected from 41,000 infusion-urograms done on men during their reproductive years. Calculation of probabilities of malignancy-induction from radiation requires some simplifying assumptions. The dose-response curve is assumed to be linear in the region of interest, and dose-fractionation is ignored. The av organ dose is used for calculation. Risk of cancer death from exposure to 1 rem varies from 2×10^{-5} deaths from exposure of bone marrow or lung to 10^{-4} for whole-body or gonad exposure. Because the usual latent period for induction of malignancy is 7-30 yr, there is little risk for persons >80 yr old. Genetic risk does not exist for those beyond reproductive age. Genetic risk is lower for children before sexual maturation than for adults. Observable increases in genetic damage from the current level of diagnostic x-rays are not predicted by these calculations. (16 refs)

- 79-5690 Lung Cancer in Man in Relation to Different Time Distribution of Radiation Exposure. (Eng) Kunz, E. (Dept. Radiation Hygiene, Inst. Hygiene and Epidemiology, 100 42 Praha 10, Czechoslovakia); Sevc, J.; Placek, V.; Horacek, J. *Health Phys* 36(6): 699-706; 1979.

The relationship between lung cancer and duration of exposure to radiation was studied among a large group of uranium miners who were exposed to radon daughter products between 1948 and 1975. Except for adenocarcinoma, the frequency of all histologic types of lung cancer was elevated in the entire group, the small cell and epidermoid types being particularly frequent. The relationship between cumulative exposure and increased cancer frequency was linear throughout the entire course of exposure only among the men with the longest exposure times. The less-increased cancer frequencies among men with shorter exposure times was related to a relatively lower incidence of the small cell undifferentiated type of cancer. In one group of men, among whom exposures were initially low and then later increased, a significant decrease in the frequency of lung cancer in the highest exposure category was also due primarily to a decrease in the small cell undifferentiated type. (16 refs)

- 79-5691 The Significance of Small Bowel Resistance to Tumor Growth: An Experimental Study. (Eng) Ortiz, V. N. (Div. Pediatric Surgery, Dept. Surgery, Ohio State Univ. Coll. Medicine, Columbus, OH 43205). *J Surg Res* 26(6): 693-697; 1979.

The mechanisms of the different patterns of bowel resistance to tumor growth were investigated using weanling and adult female Wistar rats and the Walker 256 carcinosarcoma. In adult rats sutured with material previously embedded in tumor fluid, tumor occurred in only 10% of ileoileal anastomoses, compared with 80%-90% of colocolic anastomoses and 30%-33% of ileocolostomies. Tumor growth to >1 cm in size occurred in 50% of the colocolostomies, 16% of the ileocolostomies, and none of the ileoileostomies. There was little difference in the flora of the animals at surgery or autopsy. Tumor growth occurred mainly in the submucosa at the suture line. In weanling rats implanted with

sutures previously treated with tumor fluid, tumor growth was observed in 60% of treated colons and only 10% of treated small bowels. In adults implanted sc with homogenates of large or small bowel mixed with tumor fluid, tumor growth was inhibited by the small bowel homogenate and unaffected by the large bowel homogenate or saline. The data indicate that the small bowel inhibits the growth of implanted tumor and that the inhibitory effect is in the wall of the small bowel. (3 refs)

- 79-5692 Psoralen-DNA Cross-linking Photoadducts in Dyskeratosis Congenita: Delay in Excision and Promotion of Sister Chromatid Exchange. (Eng) Carter, D. M. (Dept. Dermatology, Yale Univ. Sch. Medicine, New Haven, CT 06510); Pan, M.; Gaynor, A.; McGuire, J. S.; Sibrack, L. *J Invest Dermatol* 73(1): 97-101; 1979.

The responses of cultured fibroblasts and peripheral WBC from normal persons and two unrelated young adult men with dyskeratosis congenita (DC) were compared following exposure of the cells to 4,4',8-trimethylpsoralen (TMP) and UV light (UVL). DNA from DC cells exposed to TMP and UVL resembled DNA from normal cells with respect to patterns of sedimentation on alkaline sucrose gradients. DNA from treated cells sedimented more rapidly than that from untreated cells, and DNA from DC cells incubated for 24 hr in labeled medium after exposure to TMP and UVL still sedimented more rapidly than DNA from untreated cells. The number of sister-chromatid exchanges (SCE's) increased in WBC from normal persons and DC patients after exposure to TMP and UVL, the increase being dose-dependent in the case of the DC cells. The increase in SCE's was consistently greater for DC than for similarly treated normal cells. Treatment with psoralen or UVL alone did not affect SCE rates in DC cells. SCE values in the cells from a clinically normal brother of one DC patient resembled those from normal cells after TMP and UVL treatment, whereas the SCE values from the patient's mother were intermediate between the normal and DC values. The data are consistent with the concept that a defect in the ability to repair DNA cross-links is a fundamental abnormality in DC. (32 refs)

- 79-5693 Establishment and Characterization of C-Type RNA Virus-producing Cell Lines from Radiation-induced Murine Osteosarcomas. (Eng) Erfle, V. (Gesellschaft für Strahlen- und Umweltforschung mbH München, Institut für Biologie, D-8042 Neuherberg, W. Germany); Schulte-Overberg, S.; Marquart, K. H.; Adler, I. D.; Luz, A. *J Cancer Res Clin Oncol* 94(2): 149-162; 1979.

Eight cell lines established from murine osteosarcomas induced in vivo with the radionuclides ^{224}Ra and ^{227}Th were compared with respect to ultrastructure, karyotype, and growth properties. All cultures showed spindle-shaped cells, often in the form of cell clusters that tended to pile up. Criss-crossing was common, and pleomorphic polygonal and multinucleated giant cells were also seen. Chromosome studies revealed only mouse chromosomes with diploidy in six lines and hypotetraploidy in two. Karyotypes of the cells of four lines suggested a monoclonal origin of the cultures. Plating efficiencies, doubling times, growth in soft agar, and tumorigenicity in newborn and adult syngeneic mice indicated that five of the lines were tumor cell lines. All five cell lines contained marker chromosomes. The osteosarcoma cells of the tumor cell lines released particles into the medium that had typical properties of RNA tumor viruses: they possessed a C-type morphology, a density of 1.16-1.19 g/cm³, a 60S-70S RNA, and an

RNA-dependent DNA polymerase, and they induced syncytia in rat XC cells. (33 refs)

- 79-5694 Determination of the Uranium Content in Some Indian Cigarettes. (Eng) Chakarvarti, S. K. (Dept. Applied Physics, Regional Engineering Coll., Kurukshetra 132119, India); Dhiman, J.; Nagpaul, K. K. *Health Phys* 36(5): 638-640; 1979.

The average total uranium content of tobacco from 20 brands of Indian cigarettes as determined by a particle track etch technique was 0.04-0.1 µg/g. (9 refs)

- 79-5695 Lung Cancer Arising in Scars from Previous Thoracic Trauma. (Ita) Chiarelli, P. (Servizio di Radiologia, Ospedale Generale Provinciale, Via S. Fermo 1, 35042 Este, Padua, Italy); Carrara, M. *Radiol Med (Torino)* 65(4): 235-240; 1979.

Among a series of 60 patients with lung carcinoma, 13 had suffered previous thoracic trauma with or without rib fractures. This finding lends support to the theory that scar tissue may predispose to the development of carcinoma. (12 refs)

- 79-5696 Hepatoblastoma in a 36-Week Fetus. (Ita) Rua, S. (Servizio di anatomia ed istologia patologica, Ospedale Civile S. Croce di Cuneo, Cuneo, Italy); Olivieri, P.; Vucusa, C. *Pathologica* 71(1012): 273-278; 1979.

A hepatoblastoma was discovered in a fetus that died during the 36th wk of pregnancy. The mother had undergone x-ray examination of the abdomen and gallbladder on the 23rd day of pregnancy. She was not aware of her pregnancy at that time. The radiation and the contrast medium used for the cholecystography may have been involved in the etiology of this tumor. (29 refs)

- 79-5697 A Metabolic Model for Polonium. (Eng) Bernard, S. R. (Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). *Health Phys* 36(6): 731-732; 1979.

A polonium metabolic model for use in internal dose estimation work was developed using previously reported animal experimental data on ^{210}Po and human excretion data. (6 refs)

See also:

- *(Rev.): 79-5419, 79-5420, 79-5421, 79-5433, 79-5444, 79-5445, 79-5446, 79-5447, 79-5448, 79-5449, 79-5450, 79-5451, 79-5452, 79-5453.
- *(Chem.): 79-5513, 79-5581, 79-5603, 79-5605.
- *(Viral): 79-5734, 79-5754, 79-5797.
- *(Immun.): 79-5834.
- *(Path.): 79-5885.
- *(Epid.-Biom.): 79-5927, 79-5930, 79-5933, 79-5934, 79-5974.

VIRAL CARCINOGENESIS

- 79-5698 Direct Method of Deriving Cultures of Chick Embryo Cells Not Producing the Group-specific Antigen of Avian Leukemia Viruses. (Rus) Shmel'kova, V. I. (Lab. Biochemistry, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Kuznetsov, O. K.; Batrakova, V. P.; Fedorova, S. M.; Sokolova, A. N. *Vopr Onkol* 25(6): 125-126; 1979.

A direct method of assaying avian leukemia virus contamination in cultures of chicken embryo fibroblasts (CEF) is described. The assay consists of collecting blood samples from the embryo, preparing and then inactivating the sera, and testing the sera by a complement fixation reaction. Cultures of CEF were obtained that did not produce the group-specific antigen of avian leukosis viruses. The technique was significantly more effective than the conventional complement-fixation (COFAL) test. (5 refs)

- 79-5699 *Gs*, an Allele of Chickens for Endogenous Avian Leukosis Viral Antigens, Segregates with *ev* 3, a Genetic Locus That Contains Structural Genes for Virus. (Eng) Astrin, S. M. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Robinson, H. L. *J Virol* 31(2): 420-425; 1979.

Gs is an allele of chickens for the expression of endogenous avian leukosis virus-related core (*gs*) and envelope (*chf*) antigens. Progeny of a genetic cross in which *Gs* was segregating were analyzed for endogenous viral DNA and for the expression of endogenous viral antigens. Viral genetic information was identified by the cleavage of embryo DNA with restriction endonucleases, electrophoretic separation of the resulting fragments, and identification of bands containing viral sequences by hybridization of the DNA to ³²P-labeled viral RNA. Four different chromosomal sites of residence of endogenous viral sequences were identified. These sites were the same as those previously assigned to the endogenous viral loci *ev* 1, *ev* 3, *ev* 4, and *ev* 5. *ev* 1 was present in all of the progeny of the cross. *ev* 3, *ev* 4, and *ev* 5 were present in various combinations with *ev* 1. *ev* 3 cosegregated with the *gs***chf** phenotype. Cells that did not contain *ev* 3 but contained *ev* 1, *ev* 4, and/or *ev* 5 did not express detectable levels of viral antigens. It is suggested that *gs* contains the structural genes for endogenous virus that reside at *ev* 3 and that these structural genes code for *gs* and *chf* in *gs***chf** cells. (31 refs)

- 79-5700 Chromatin Alterations and Gene Function Disorder in MC-29 Virus-derived Hepatoma. (Eng) Jeney, A. (First Inst. Pathology, Semmelweis Medical Univ., Budapest, Hungary); Kovalszky, I.; Gyapay, G.; Lapis, K.; Suba, Z. *J Toxicol Environ Health* 5(2/3): 509-516; 1979.

The effect of dexamethasone on DNA and RNA synthesis and the composition of chromatin was analyzed in MC-29 virus-derived transplantable hepatoma (VTH) in chickens. Dexamethasone was administered ip (1 mg/g body wt) for 6 hr. Nucleic acids were labeled during the final hr of dexamethasone treatment with [6-³H]-thymidine or [5-³H]-uridine. In VTH, DNA and RNA labeling were both higher after dexamethasone treatment: 56.6 ± 4.2 in

controls increased to 82.0 ± 11.8 in treated tumors for DNA; and 24.3 ± 3.9 in controls increased to 37.9 ± 6.2 in treated tumors for RNA. In normal chicken liver, DNA and RNA labeling decreased after dexamethasone treatment. Compared with the amounts in normal liver, acidic chromatin proteins designated as the 0.35 M NaCl soluble fraction and nonhistones were increased and the histones were decreased in VTH. A remarkable variation in the distribution pattern of nonhistones was observed with sodium dodecyl sulfate-polyacrylamide gel electrophoresis. When the amount of unique and repetitive DNA segments per cell was estimated, it was shown that the elevation in total DNA in VTH compared with normal liver results mainly from the repetitive segments, which increased by 200%, while the unique segments increased only 40%. It is shown that structural alteration of the receptor or chromatin components influencing the binding of regulatory molecules to DNA may be important in the damaged function of glucocorticoids in the VTH. The structural alterations of chromatin nonhistones may be responsible for the lack of physiological responses to steroids with VTH, and the increased proportion of repetitive DNA sequences may be a characteristic of the disorder of gene regulation in malignant cells. (11 refs)

- 79-5701 Histology and Ultrastructural Aspects of Virus-induced Primary Liver Cancer and Transplantable Hepatomas of Viral Origin in Chickens. (Eng) Lapis, K. (First Inst. Pathology, Semmelweis Medical Univ., Budapest, Hungary). *J Toxicol Environ Health* 5(2/3): 469-501; 1979.

The macroscopic, light microscopic, and electron microscopic features and biological properties of MC-29 leukosis virus-induced hepatocellular carcinomas in chickens are described. The tumors developed in noncirrhotic livers within a very short time and formed metastases. The various histological types of tumors observed were very similar to those of human tumors. The presence of C-type viruses, especially in the intercellular spaces and bile capillaries, and signs of virus production were evidenced in the tumors. There were also indications of virus production in the transplantable tumors, which had a take rate of >90% and grew equally well after sc, ip, or im inoculation. In 6%-8% of the tumor cells, cytoplasmic inclusion bodies composed of peculiar undulating membranous structures appeared. Tumorous nodules developed in the liver of about 25% of the tumor-bearing animals. It could not be established whether they were metastases or primary liver cancers induced by viruses released from the transplantable tumors. (137 refs)

- 79-5702 Comparative Study of Tumor-specific Transplantation Antigens of MC-29 Chicken Hepatoma and Rous Sarcoma Virus-induced Sarcomas in Mice. (Eng) Elek, G. (First Inst. Pathology, Semmelweis Univ., Budapest, Hungary); Lapis, K.; Foldes, I. *J Toxicol Environ Health* 5(2/3): 529-536; 1979.

The take rate and growth of transplantable sarcomas induced by Rous sarcoma virus, Schmidt-Ruppin strain [RSV(SR)], were analyzed in syngeneic mice immunized with antigen prepared from a MC-29 virus-induced chicken hepatoma and in control syngeneic

mice. Immunization of CBAT6T6 mice with chicken MC-29 hepatoma antigen did not change the number of takes of RSV(SR) tumors after sc transplantation. Immunization only slightly increased the av survival time of the mice, and it significantly decreased tumor growth only at the minimum lethal dose level. Immunization of mice with MC-29 hepatoma antigen and with chicken Rous sarcoma antigen gave similar results; both elicited much less transplantation resistance than immunization with irradiated RSV(SR) tumor cells. The data indicate that there are common tumor-specific transplantation antigens of MC-29 hepatoma and Rous sarcoma, but further in vitro experiments are needed to prove this. (23 refs)

- 79-5703 Biochemical Behavior of MC-29 Virus-induced Transplantable Chicken Hepatoma. (Eng) Prajda, N. (Natl. Inst. Oncology, Budapest, Hungary); Eckhardt, S.; Suba, Z.; Lapis, K. *J Toxicol Environ Health* 5(2/3): 503-508; 1979.

The applicability of the molecular correlation concept developed for chemically induced transplantable rat hepatomas to virally induced transplantable hepatomas in chickens was tested. In the experimental group, transplantable MC-29 virus-induced hepatomas were maintained in Hunnia hybrid chickens for 10 days. The animals were decapitated, their livers and hepatomas were homogenized, and protein content and enzyme contents were analyzed. The following enzymes were assayed: hexokinase (HK), pyruvate kinase (PK), glucose-6-phosphatase (G6P), glucose-6-phosphate dehydrogenase (G6PDH), thymidine kinase (TK), glutamine phosphoribosylpyrophosphate amidotransferase (G-PRPP-AT) and xanthine oxidase (XO). When compared with enzyme activities in the rat, the chicken liver enzymes were as follows: HK, 133%; PK, 88%; G6P, 175%; G6PDH, 25%; TK, 277%; G-PRPP-AT, 1,355%; and XO, 29%. In chemically and virally induced rapidly growing hepatomas, the pattern of neoplastic alterations was similar: the activities of the glycolytic enzymes were increased and those of the gluconeogenic enzyme were decreased in both tumors. In both types of tumor the increases in the activities of G6PDH and TK were observed; G-PRPP-AT activity increased, while that of XO decreased. In the hepatoma, the enzymatic imbalance was completely different from the pattern in differentiating liver and thus seems to be specific for the neoplastic transformation. (14 refs)

- 79-5704 Influence of Immune Status on Virus-Derived Transplantable Hepatoma in Chickens. (Eng) Foldes, I. (Microbiological Res. Group, Hungarian Acad. Sciences, Budapest, Hungary). *J Toxicol Environ Health* 5(2/3): 517-528; 1979.

The transplantable MC-29 virus-induced chicken hepatoma was used as an experimental model to investigate the effect of immune status on virus-derived transplantable hepatoma. Surgical bursectomy and thymectomy were performed on groups of Hunnia hybrid or White Leghorn chickens; then tumor homogenate was transplanted on the same day, or 7 or 14 days thereafter. No differences in tumor take were observed when the tumor was transplanted on the day of hatching. When the transplantation occurred on day 7 after hatching, the thymectomized birds succumbed earlier. When tumors were transplanted on day 14, bursectomy and thymectomy increased the frequency of tumor take. Tumorigenesis could not be influenced by the adoptive transfer of immune serum and immune cells in this tumor system. Tumor growth was inhibited but not prevented by the administration of

live BCG or strain W-115 of *Mycobacterium tuberculosis* together with the tumor transplant. When the hepatoma was transplanted into newly hatched chickens and the birds were killed 10 or 14 days thereafter, the weight of the bursa of Fabricius and the thymus decreased in the tumor-bearing animals; and a marked decrease in the thymus cells was observed. In normal birds, dexamethasone markedly induced hepatic tyrosine aminotransferase (TAT), while no detectable change was observed in tumor-bearing birds. This difference indicates that the mechanism of control of protein synthesis was impaired in the early phase of tumor development. Glucagon increased the TAT activity in both normal and tumor-bearing chickens. When glucocorticoid hormones were administered twice in 48 hr, an 80% decrease in thymidine kinase activity was observed in the thymus lobes of healthy chickens, while no response was observed in the tumor-bearing chickens. In cell-free systems prepared from thymus lobes of tumor-bearing chickens, a significant decrease in the steroid binding capacity was observed. (12 refs)

- 79-5705 DNA Endonucleases Associated with the Avian Myeloblastosis Virus DNA Polymerase. (Eng) Samuel, K. P. (Dept. Human Genetics and Development, Coll. Physicians and Surgeons, Columbia Univ., 630 W. 168 St., New York, NY 10032); Papas, T. S.; Chirikjian, J. G. *Proc Natl Acad Sci USA* 76(6): 2659-2663; 1979.

Two endonucleases that are present in avian myeloblastosis virus cores and use superhelical DNA's as substrates are described. DNA endonuclease Endo-I was isolated from avian myeloblastosis virions stripped of their coats by mild detergent treatment. The enzyme has a broad pH optimum around 7.5-8.0 and requires Mg^{2+} for activity. A second endonuclease, Endo-II, with a requirement for Mn^{2+} , was also present in the viral cores. It copurified with avian myeloblastosis virus $\alpha\beta$ DNA polymerase (reverse transcriptase, RNA-dependent DNA nucleotidyltransferase) and similarly cleaved superhelical DNA's. Heat denaturation and sodium fluoride- and N-ethylmaleimide inhibition studies were carried out to demonstrate a possible relationship between the two endonucleases and the viral DNA polymerase and RNase H activities. It appears that Endo-II may be an intrinsic activity of the polymerase. (24 refs)

- 79-5706 Stimulation of Sugar Uptake and Glycolysis in Chicken Embryo Fibroblasts by the Major Glycoprotein from Avian Myeloblastosis Virus. (Eng) Papamatheakis, J. D. (Lab. Tumor Virus Genetics, NCI, NIH, Bethesda, MD 20205); Marciani, D. J. *Proc Natl Acad Sci USA* 76(6): 2784-2788; 1979.

The occurrence of significant changes in glucose transport and glycolysis in normal chicken embryo fibroblasts (CEF) after treatment of these cells with the highly purified major glycoprotein (gp) from avian myeloblastosis virus (AMV) is reported. Addition of the gp to growing or quiescent CEF rapidly stimulated the rate of hexose transport and increased lactic acid production. These stimulatory effects were dependent on the time of exposure and the dose of viral gp. In contrast, the gp only marginally affected hexose transport in chicken cells transformed by Rous sarcoma virus. Some effects of the gp on serum-starved quiescent cells were similar to those observed upon readdition of serum; however, the viral gp did not stimulate DNA synthesis. Quiescent cells stimulated by saturating levels of serum showed little further stimulation of hexose uptake upon exposure to viral gp for 3 hr. This behavior suggests that the gp may be acting on a system that is also a target for serum action. (21 refs)

- 79-5707 Cellular Information in the Genome of Recovered Avian Sarcoma Virus Directs the Synthesis of Transforming Protein. (Eng) Karess, R. E. (Rockefeller Univ., New York, NY 10021); Hayward, W. S.; Hanafusa, H. *Proc Natl Acad Sci USA* 76(7): 3154-3158; 1979.

The presence of information directing the production of transforming protein (p60^{src}) in avian sarcoma viruses (rASV's) recovered from chicken tumors was investigated. Immunoprecipitation of chicken embryo fibroblasts infected with different rASV's with serum raised in rabbits bearing regressing tumors induced by the Schmidt-Ruppin strain of ASV, subgroup D (SR-D), revealed that a protein migrated with the p60^{src} of subgroup A virus (SR-A). The p60^{src} from rASV was a phosphoprotein. The p60^{src} from cells infected with different rASV's and the p60^{src} from normal cells showed nearly identical proteolytic digestion patterns. Immunoprecipitates of p60^{src} from rASV-infected cells possessed protein kinase activity. The amounts of p60^{src} obtained from cells transformed with rASV 1441 or SR-A were similar, whereas the amount recovered from untransformed cells was 100- to 200-fold less. The amounts of *src*-specific messenger RNA's were correlated with the amounts of p60^{src} and p60^{src} in transformed and normal cells. (30 refs)

- 79-5708 Transformation of NIH/3T3 Mouse Cells by DNA of Rous Sarcoma Virus. (Eng) Copeland, N. G. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115); Zelenetz, A. D.; Cooper, G. M. *Cell* 17(4): 993-1002; 1979.

To determine whether previously observed differences in the mechanisms of transfection of chicken cells by Rous sarcoma virus (RSV) DNA and of mouse cells by murine sarcoma virus (MSV) DNA were due to differences in the recipient cells or to differences in the virus DNAs, transformation of NIH/3T3 mouse cells by RSV DNA was investigated. The mouse cells were transformed by integrated and unintegrated DNAs of RSV-infected chicken cells without production of progeny virus. In addition, DNA of the replication-defective Bryan high titer strain of RSV transformed NIH/3T3 cells, indicating that transformation of NIH/3T3 cells by RSV DNA did not require virus replication. The efficiency of transformation of NIH/3T3 cells by RSV DNA was similar to the efficiency of transformation of these cells by murine sarcoma virus DNA and to the efficiency of transfection of chicken embryo fibroblasts by RSV DNA. NIH/3T3 cells transformed by RSV DNA were morphologically similar to cells transformed by virus infection and were capable of anchorage-independent growth in soft agar. Stable inheritance of intact RSV genomes by RSV DNA-transformed NIH/3T3 cells were demonstrated by rescue of virus from these cells after fusion with chicken embryo fibroblasts and by transfection assays of the DNAs of RSV DNA-transformed NIH/3T3 cells on chicken embryo fibroblasts. Analysis of the DNAs of RSV DNA-transformed NIH/3T3 cells by restriction endonuclease digestion and nucleic acid hybridization indicated that RSV genomes were linked to cellular DNA sequences. It therefore appeared that transformation of NIH/3T3 cells by RSV DNA occurred by direct integration and stable expression of the donor DNA, rather than by production of extracellular progeny virus and secondary virus infection. (33 refs)

- 79-5709 Analysis of the Specificity of Integration of Provirus DNA of Rous Sarcoma Virus into DNA of Transformed Rat Cells. (Rus) Farashian, V. R. (D. I. Ivanovskii Inst. Virology, Moscow, USSR); Gudkov, A. V.; Naroditskii, B.

S.; Obukh, I. B.; Tikhonenko, T. I.; Zhdanov, V. M. *Dokl Akad Nauk SSSR* 247(4): 967-970; 1979.

An attempt was made to determine the localization of virus-specific sequences of Rous sarcoma virus (RSV) in the DNA of transformed rat cells (DNA_{xc}). The XC cell line was derived from rat tumor induced by RSV (Prague strain, substrain C). DNA_{xc} hydrolysis using a series of endonucleases (R x *EcoRI*, R x *SalI*, R x *BamHI*) revealed a number of fragments with mol wt ranging from 0.5 to 20 megadaltons. It was suggested that the low mol wt fragments (0.6 and 0.9 megadaltons) correspond to internal regions of the provirus, while the group of fragments with mol wt ranging from 2.9 to 9 megadaltons may correspond either to the terminal fragments of provirus DNA combined with various cellular sequences, or to several proviruses that are tandemly incorporated into DNA_{xc}, or to several defective proviruses with deletions of various sizes. (15 refs)

- 79-5710 Suppression of Multiplication of Avian Sarcoma Virus by Rapid Spread of Transformation-defective Virus of the Same Subgroup. (Eng) Estis, L. F. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Temin, H. M. *J Virol* 31(2): 389-397; 1979.

A subgroup A avian sarcoma virus (ASV-A) that does not contain transformation-defective (*td*) virus and an independently isolated *td*ASV-A were used to test the hypothesis that some *td* viruses grow faster than the ASV's from which they are derived, resulting in establishment of interference by the *td* virus and suppression of ASV multiplication. At multiplicities of one or less in vitro, *td*ASV alone grew to higher titers and more rapidly than ASV alone. In mixed infections at low multiplicities that allowed the spread of progeny virus and with as little as 10% of the inoculum being *td* virus, there was an excess of *td* virus by 2 days after infection and a decrease in the titer of ASV relative to a control infection with no *td* virus. In mixed infections at high multiplicities that minimized the spread of progeny virus, there was no excess of *td* virus and the ASV titer was not decreased relative to the control infection. There was no simple correlation between the amounts of unintegrated viral DNA early after infection and the titers of virus produced, indicating perhaps that virus production was determined by integrated viral DNA. The data support the proposed hypothesis and indicate that deletions in the ASV *src* gene may not be a high-frequency event. (26 refs)

- 79-5711 Hybridization Analysis of Viral Nucleotide Sequences in the DNA of Hamster Rous Sarcoma. (Rus) Ratovitskii, E. A. (Lab. Biochemistry, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Shaposhnikov, Ia. D.; Korobitsin, L. P.; Gaber, V. K.; Blank, M. A.; Neishtadt, E. L. *Vopr Onkol* 25(6): 52-54; 1979.

An attempt was made to determine whether the DNA of hamster Rous sarcomas (induced by inoculation of hamsters with suspensions of chicken Rous sarcoma cells) contains the nucleotide sequence of virus RNA. Inoculation of chicks with a suspension of hamster tumor cells failed to induce tumors, which indicates that the hamster tumor does not produce Rous sarcoma virions. On the other hand, the hamster sarcoma cells contained the group-specific antigen of avian oncornavirus. Molecular hybridization of the viral RNA with DNA isolated from the hamster tumor cells showed that viral information was located in the region of moderately redundant and unique sequences of tumor DNA. (5 refs)

79-5712 Declining Procollagen mRNA Sequences in Chick Embryo Fibroblasts Infected with Rous Sarcoma Virus. (Eng) Sandmeyer, S. (Dept. Biochemistry, Univ. Washington, Seattle, WA 98195); Bornstein, P. *J Biol Chem* 254(12): 4950-4953; 1979.

The kinetics of the decrease in procollagen biosynthesis and in procollagen messenger RNA (mRNA) sequences during the first 84 hr after infection of chick embryo fibroblasts with Rous sarcoma virus (RSV) were investigated. Whether the initial reduction in procollagen synthesis could be attributed to the events which affect the concentration of the message or to factors altering the activity of the mRNA was studied. The time course of the decrease in procollagen biosynthesis was measured by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and collagenase assay and compared with the decrease in procollagen mRNA sequences measured by hybridization to a complementary DNA (cDNA). Procollagen synthesis declined starting 24 hr after infection and continued to decline 84 hr after infection. In cells not infected with RSV procollagen synthesis increased during the same time period. After RSV infection a decline was observed in the procollagen sequences 24 hr postinfection and continued in parallel with the change in procollagen synthesis up to 84 hr. In uninfected cells, the level of procollagen mRNA levels increased significantly until 36 hr, when it reached a plateau and returned to initial levels by 84 hr. Electrophoresis of (2,3-³H)proline-labeled protein in chick embryo fibroblasts after RSV infection demonstrated a decrease in the density of the bands comigrating with pro α 1(I) and pro α 2 chains over the time course. At 48 hr postinfection, radioactivity in the two procollagen bands of the transformed cells was 43% of that in the control group. Transformed cell procollagen bands had decreased to 14% of the control value by 84 hr. Thus, even the initial decrease in procollagen biosynthesis was due to a decline in the level of procollagen mRNA. (28 refs)

79-5713 Mutants of Rous Sarcoma Virus with Extensive Deletions of the Viral Genome. (Eng) Martin, G. S. (Dept. Zoology, Univ. California, Berkeley, CA 94720); Radke, K.; Hughes, S.; Quintrell, N.; Bishop, J. M.; Varmus, H. E. *Virology* 96(2): 530-546; 1979.

Deletion mutants of Rous sarcoma virus (RSV) were isolated from a stock of Prague RSV that had been irradiated with UV light. Quail fibroblasts were infected with irradiated virus, and transformed clones were isolated by agar suspension culture. Three clones were obtained that did not release any virus particles. Analysis of DNA from these nonproducer clones with restriction endonucleases and the Southern DNA transfer technique indicated that the clones carry defective proviruses with deletions of approx 4×10^6 daltons of proviral DNA. The defective proviruses, which retain the viral transformation (*src*) gene, contain only $1.7\text{--}2.0 \times 10^6$ daltons of DNA. Multiple species of viral RNA containing sequences of the *src* gene were detected in these clones; some of these RNA's may contain both viral and cellular sequences. The protein product of the *src* gene, p60^{src}, was also synthesized in the nonproducer clones. However, these clones did not contain the products of the group-specific antigen (*gag*), DNA polymerase (*pol*), or envelope glycoprotein (*env*) genes, nor did they contain the 35S and 28S RNA species that are believed to represent the messengers for these viral gene products. The properties of these mutants indicate that expression of the *src* gene is sufficient for the induction of transformation. These clones may be useful in studies of the expression of this region of the genome. (44 refs)

79-5714 Studies of the Effect of Chloramphenicol, Ethidium Bromide and Camptothecin on the Reproduction of

Rous Sarcoma Virus in Infected Chick Embryo Cells. (Eng) Leblond-Larouche, L. (Institut du Cancer de Montreal, Centre Hospitalier Notre-Dame, Montreal, Quebec, Canada); Morais, R.; Zollinger, M. *J Gen Virol* 44(2): 323-331; 1979.

The effects of chloramphenicol (CAM), ethidium bromide (EB), and camptothecin (CN) on the reproduction of Rous sarcoma virus (RSV) in infected chick embryo fibroblasts (CEF) were studied to determine the role of mitochondria in RSV reproduction. In the presence of 80 $\mu\text{g/ml}$ CAM, the population doubling time of RSV-infected CEF increased initially, and then decreased significantly. EB (0.4 $\mu\text{g/ml}$) also decreased the cell growth rate, and CN (4.0 $\mu\text{g/ml}$) proved to be a potent inhibitor of cell division. Leucine, thymidine, and uridine incorporation into total cell macromolecules was unaffected by CAM, inhibited by 20%-44% by EB, and inhibited 35%-50% by CN. Mitochondrial translation in RSV-infected CEF was totally inhibited by 80 $\mu\text{g/ml}$ CAM, and labeled leucine incorporation into mitochondrial proteins was reduced. EB also inhibited the synthesis of proteins coded for by mitochondrial DNA (mDNA), whereas CN did not inhibit the incorporation of leucine and thymidine into mitochondrial proteins and mDNA, respectively. CAM and EB did not inhibit, and may have increased, virus production by RSV-infected cells, whereas CN did inhibit the production of infectious virus. The results indicate that the mitochondrial macromolecular synthetic machinery of RSV-infected CEF does not contribute to virus production. (40 refs)

79-5715 High-Frequency Recombination Within the *gag* Gene of Rous Sarcoma Virus. (Eng) Linial, M. (Div. Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Brown, S. *J Virol* 31(1): 257-260; 1979.

Twenty-eight recombinants of Rous sarcoma virus were isolated 1 and 7 days after infection, selected for wild type in the *pol* and *src* genes, and analyzed for their *env* and *gag* phenotypes. A strong linkage between any two markers, including two within a single gene (*gag*), could not be shown. (20 refs)

79-5716 Use of Recombinant Plasmids to Characterize Collagen RNAs in Normal and Transformed Chick Embryo Fibroblasts. (Eng) Adams, S. L. (Lab. Molecular Biology, NCI, NIH, Bethesda, MD 20205); Alwine, J. C.; de Crombrughe, B.; Pastan, I. *J Biol Chem* 254(12): 4935-4938; 1979.

Two recombinant plasmids (pCOL1 and pCOL3) containing chick collagen DNA sequences were used to characterize messenger RNA's (mRNA's) for pro- α 1 (type 1) and pro- α 2 collagen, to identify two larger RNA species that contain pro- α 1 and pro- α 2 collagen RNA sequences, and to compare the amounts of these collagen-specific RNA's in normal chick embryo fibroblasts (CEF) and CEF transformed by Rous sarcoma virus. pCOL3 DNA retains only pro- α 1 collagen mRNA and pCOL1 DNA retains only pro- α 2 collagen mRNA. Poly(A)-containing RNA from chick embryo calvaria and long bones, tissues that are very active in collagen synthesis, were electrophoresed on agarose gels containing methylmercuric hydroxide and transferred to diazobenzyloxymethyl paper; these covalently bound RNA's were hybridized to ³²P-labeled pro- α 1 or pro- α 2 collagen DNA sequences derived from the recombinant plasmids. The pro- α 1 collagen probe identified two RNA's, a major species of 5,000 bases and a minor species of 7,100 bases. The pro- α 2 collagen probe hybridized to a major species very similar in size to the pro- α 1 mRNA, about

5,200 bases, and a minor species of 5,700 bases. It is possible that the 7,100- and 5,700-base RNA's represent precursors of pro- $\alpha 1$ and pro- $\alpha 2$ collagen mRNA, respectively. When similar hybridization experiments were performed with RNA from CEF, both the pro- $\alpha 1$ and pro- $\alpha 2$ collagen mRNA's were observed, as well as their corresponding larger species. With RNA's from CEF transformed by Rous sarcoma virus, however, the levels of all RNA species that hybridized with the pro- $\alpha 1$ and pro- $\alpha 2$ collagen DNA probes were significantly reduced. (31 refs)

- 79-5717 New Procedure for Isolation of Rous Sarcoma Virus-specific RNA from Infected Cells. (Eng) Bromley, P. A. (Departement Biologie Moleculaire, Universite de Geneve, CH-1211 Geneva 4, Switzerland); Spahr, P. F.; Darlix, J. L. *J Virol* 31(1): 86-93; 1979.

The use of mercurated 'strong stop' complementary DNA (complementary to the 5'-terminal 101 nucleotides of Rous sarcoma virus RNA) in the isolation of virus-specific RNA from infected chicken embryo fibroblasts is described. Strong stop Rous sarcoma virus complementary DNA was mercurated chemically, and, as a result of the low complexity of this DNA, short hybridization times (up to 15 min) and heating in the absence of formamide were found to be adequate conditions for the isolation of virus-specific RNA. The purity of the isolated RNA was demonstrated by analysis of labeled RNase T1-resistant oligonucleotides by two-dimensional polyacrylamide gel electrophoresis. The isolated RNA could be translated in the in vitro protein synthesis system derived from rabbit reticulocytes, and an analysis of polypeptides programmed by isolated RNA before and after immunoprecipitation further demonstrated both the purity of the isolated messenger RNA and the quantitative nature of the isolation procedure. (28 refs)

- 79-5718 Endogenous Oncornaviral Antigen in the Bursa of Fabricius of 15B x 7₂ Chickens. (Eng) England, J. M. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Halpern, M. S. *Proc Natl Acad Sci USA* 76(6): 2908-2911; 1979.

Because infection of chickens with exogenous leukosis viruses specifically induces a B-cell lymphoma that arises in the bursa of Fabricius, the distribution of endogenous oncornaviral antigen in the bursas of 15B x 7₂ chickens was investigated. These chickens spontaneously produce high levels of Rous-associated virus type 0. Oncornaviral antigen was detected in the bursal epithelium and in a subpopulation of bursal follicular cells of the chickens. This antigen was present in the bursal epithelium at 11 days of embryogenesis and persisted there for at least 3 wk after hatching. The absence of detectable antigen in the intestinal epithelium contiguous to the bursal epithelium indicates that the accumulation of viral antigen is a specific property of the bursal epithelium. The observation of C-type particles in the intraepithelial spaces suggests that the viral antigen is synthesized and assembled into virions by the bursal epithelial cells. In embryonic bursas, viral antigen-positive cells radiated from the surface epithelium toward the central region of the follicles. In bursas from posthatch chickens, viral antigen-positive cells, including intrafollicular epithelial cells and cells resembling lymphocytes, were confined to the medullary region of the follicles. (21 refs)

- 79-5719 Isolation and Development of a Reticuloendotheliosis Virus-transformed Lymphoblastoid Cell Line from Chicken Spleen Cells. (Eng) Keller, L. H. (Dept. Veterinary and Animal Sciences, Univ. Massachusetts, Amherst, MA 01003); Rufner, R.; Sevoian, M. *Infect Immun* 25(2): 694-701; 1979.

The in vitro establishment and characterization of a T-strain reticuloendotheliosis virus (REV-T)-transformed lymphoblastoid cell line (TV-1) derived from the spleen of a moribund SPAFA chick infected with REV-T are reported. Splenic cultures grown at 41 C were maintained in suspension culture for >74 wk, the generation time having stabilized at approx 15 hr. The optimal density for growth was 5×10^5 to 1×10^6 cells/ml. Karyotype analysis of the cells indicated the presence of a female chromosome (ZW). C-type REV-T budding virions were observed in the region of the plasma membrane, and particles characteristic of REV-T were observed extracellularly. TV-1 cells and their culture supernatant produced lesions typical of REV-T infection after inoculation into 1-day- to 1-wk-old chicks. The LD₅₀ remained constant at $10^{4.337}$ from 9 to 24 wk and then dropped to $10^{3.124}$ after 31 wk. Cytotoxicity assays and fluorescent antibody tests indicated the presence of B-cell determinants on the TV-1 cell-surface membranes. (17 refs)

- 79-5720 Lymphoid Neoplasms in Chicken Flocks Free of Infection with Exogenous Avian Tumor Viruses. (Eng) Crittenden, L. B. (Regional Poultry Res. Lab., Agricultural Res., Science and Education Admin., U.S. Dept. Agriculture, 3606 East Mount Hope Road, E. Lansing, MI 48823); Witter, R. L.; Okazaki, W.; Neiman, P. E. *J Natl Cancer Inst* 63(1): 191-200; 1979.

The hypothesis that full or partial expression of Rous-associated virus type 0 (RAV-0) is responsible for the lymphoid neoplasms in chickens free of infection with exogenous avian tumor viruses was investigated. More than 4,500 breeding female chickens of nine inbred lines maintained under specific-pathogen-free conditions to approx 500 days of age were studied. Routine monitoring and special assays indicated that they were free of infection by exogenous leukosis-sarcoma and reticuloendotheliosis viruses. Some birds were maintained free of Marek's disease (MD) virus infection in plastic isolators; and others were maintained in conventional chicken houses and vaccinated with herpesvirus of turkeys to prevent MD lesions. Ten birds bearing lymphoid tumors were observed in two sublines of a line of chickens known to produce embryos that spontaneously produce the endogenous RAV-0. Four tumors were found in chickens of one subline maintained free of MD virus infection in isolators. These tumors did not involve the bursa, and they had some histologic features different from those typical of lymphoid leukosis (LL). Six tumors were found in chickens of the other subline that were vaccinated to prevent MD; these tumors involved the bursa and were typical of LL but not MD. These results suggest that two types of tumors may have been observed. The fact that DNA from both tumor types did not contain exogenous LL virus sequences confirms the virologic evidence that exogenous viruses were not involved. The fact that endogenous viral sequences were not increased in copy number suggests that RAV-0 did not directly induce the tumors. Two birds with tumors not involving the bursa were found alive, and transplantable lymphoid tumors were developed. These tumors were of T-cell rather than bursa cell origin, as would be expected of LL. These are the first reported lymphoid tumors observed in the absence of known exogenous tumor virus infection in chickens. The evidence suggests that RAV-0 did not play a primary role in the induction of these tumors. (62 refs)

- 79-5721 Recombination Between the Defective Component of an Acute Leukemia Virus and Rous Associated Virus 0, an Endogenous Virus of Chickens. (Eng) Tschlis, P. N. (Dept. Medicine, Tufts Univ. Sch. Medicine, Boston, MA 02111); Coffin, J. M. *Proc Natl Acad Sci USA* 76(6): 3001-3005; 1979.

The ability of the defective acute leukemia virus of chickens, MC-29, to participate in recombination was investigated by testing the ability of the MC-29 genome to donate sequences to its helper virus. The endogenous virus Rous-associated virus 0 (RAV-0) was used as a helper for MC-29, and its genome was compared by fingerprinting with that of the original RAV-0. In three separate isolates, the RAV-0 used as a helper for MC-29 had acquired new sequences near the 3' and 5' ends of its genome. The new 3' proximal sequences resembled the C region found in exogenous but not endogenous avian oncoviruses, and it probably imparted a higher growth rate to the recombinant compared with that imparted by RAV-0. One isolate also showed recombination within the *env* gene. Because the possibility that the recombination was with host cell information or with the original helper of MC-29 could not be excluded, it is concluded that the acquired sequences were derived from the MC-29 genome and, therefore, that this replication-defective virus is not defective in recombination. (24 refs)

- 79-5722 Intracellular State of Marek's Disease Virus DNA in Two Tumour-derived Chicken Cell Lines. (Eng) Kaschka-Dierich, C. (Institut für Klinische Virologie, Universität Erlangen-Nürnberg, Loschgestr. 7, 852 Erlangen, W. Germany); Nazerian, K.; Thomssen, R. *J Gen Virol* 44(2): 271-280; 1979.

The intracellular state of Marek's disease virus (MDV) DNA was investigated in two permanent chicken cell lines: HPRS-1, a virus nonproductive line established from an ovarian lymphoma of a chicken with MD; and MSB-1, a low virus producer line, established from a chicken with a MD splenic lymphoma. By repeated isopycnic centrifugation in cesium chloride, MDV DNA in the HPRS-1 line showed properties of integrated DNA, whereas both integrated and free virus DNA appeared to be present in the MSB-1 cells. Under denaturing conditions (0.1 M sodium hydroxide), the virus DNA remained associated with the cellular DNA as revealed by equilibrium centrifugation in CsCl and hybridization of the DNA in each single fraction with ³²P-labeled complementary RNA (³²P-cRNA) transcribed from the DNA of the GA strain of MDV. Shearing of HPRS-1 DNA to a mol wt of 8×10^6 released only part of the virus DNA with a density similar to that of free virus DNA, while a large proportion of MDV DNA still remained associated with the cellular DNA. Sedimentation velocity experiments with HPRS-1 and MSB-1 DNA originally fractionated on CsCl gradients revealed integrated virus DNA sequences in both cell lines and an additional peak of virus DNA at the position of free linear MDV DNA in the MSB-1 line. No MDV DNA sequences sedimenting at the expected position of covalently closed circular DNA of virus genome length (100-110S) was detected in any of these experiments. It is concluded that virus integration is a general phenomenon not restricted to malignant transformation. (31 refs)

- 79-5723 Macrophage Restriction of Marek's Disease Virus Replication and Lymphoma Cell Proliferation. (Eng) Lee, L. F. (United States Dept. Agriculture, Science and Education Admin., Federal Res. Regional Poultry Res. Lab., 3606 East Mount Hope Road, East Lansing, MI 48823). *J Immunol* 123(3): 1088-1091; 1979.

Macrophage function and its mechanism of action in the host immune response were studied. Treatment of spleen cells from White Leghorn chickens infected with the GA strain of Marek's disease virus (MDV) with anti-T serum and complement (C) had no effect on virus titer, but treatment with anti-B serum and C increased virus titer two- to threefold. Treatment with carbonyl iron/magnet to remove macrophages increased the virus titer 4- to 18-fold. The level of ¹²⁵I-iodo-2'-deoxyuridine uptake into MD-lymphoma cells was about the same for virus-inoculated and control line 6, chickens. In susceptible line 7, chickens, MDV inoculation induced a fivefold increase in isotope uptake; this increase was abolished when MDV spleen cells were pretreated with anti-Marek's disease tumor-associated surface antigen serum plus C. Pretreatment with carbonyl iron/magnet to remove macrophages resulted in a 70% increase in isotope uptake by normal spleen cells, a 200% increase by those from MDV-inoculated line 7, chickens, and a 300% increase in cells from similarly inoculated line 6, chickens. The results indicate that macrophages play a significant role in the restriction of MDV replication and the regulation of lymphoma cell proliferation in spleen cells from MDV-inoculated chickens. (18 refs)

- 79-5724 Expression of Genetic Resistance to an Oncogenic Herpesvirus at the Target Cell Level. (Eng) Gallatin, W. M. (Dept. Immunology, Univ. Alberta, Edmonton, Alberta, Canada); Longenecker, B. M. *Nature* 280(5723): 587-589; 1979.

The mechanism of non-major histocompatibility complex (non-MHC) resistance to oncogenic herpesviruses was studied in vitro and in vivo. Spleen cells from Marek's disease virus (MDV)-resistant line-6 chickens and from susceptible line-7 birds were incubated with herpesvirus of turkeys (HVT) for 1 hr, and infectious centers were assayed in ovo. Line-7 spleen cells induced 6.7 times more infectious centers than did line-6 spleen cells. In the in vivo tests, line-6 and line-7 spleen cells were transferred into separate groups of irradiated, histocompatible, third-party recipients, which were then exposed to MDV. More than four times more line-7 spleen cells than line-6 cells were infected with MDV. Injection of line-7 embryonic spleen cells into line-6 embryos did not significantly increase MD mortality. However, the transplantation of line-7 thymuses into newly hatched, thymectomized line-6 recipients rendered the line-6 birds much more susceptible to MD. These data suggest that genetic resistance to an oncogenic herpesvirus can be manifested at the target cell level and that the target cell for MDV-induced transformation is a T lymphocyte. While the mechanism of resistance at the target T lymphocyte level remains unknown, the viral adsorption studies suggest that resistant birds may have target cells with fewer virus receptors, receptors of lower affinity for virus, or fewer target cells with identical receptors. (20 refs)

- 79-5725 Xenogenization of Lymphocytes, Erythroblasts, and Tumor Cells. (Eng) Kobayashi, H. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Hokkaido, Japan); Takeichi, N.; Kuzumaki, N. *Hokkaido Univ Med Lib Ser* 10: 174 pp.; 1978.

The xenogenization (the immunologic regression of tumors induced by or artificially infected with membranous viruses in syngeneic and autochthonous hosts) of lymphocytes, erythroblasts, and tumor cells is reviewed in relation to immunologic tolerance, running syndrome, and hemolytic anemia. When newborn animals are injected with a nonlytic xenogenic virus, they become im-

munologically tolerant to the virus-specific antigens (VSA). If the virus is oncogenic, leukemia occasionally develops; and if the tolerant state is not complete or if there is a gradual decrease in the unresponsiveness to VSA, the runting syndrome is occasionally seen. Rats suffering from the runting syndrome often have an autoimmune hemolytic anemia. When adult immunologically competent animals are inoculated with xenogenized tumor cells, minimal tumor growth generally occurs and the tumor undergoes regression. If the immunogen is obtained from xenogenized tumor, there is an increased immune response when compared to nonvirus-infected tumor. In vitro studies indicate that xenogenized tumor cells have an increased level of specific reactivity when compared with nonxenogenized tumor cells. The applicability of these findings to human disease is only speculative at present. (345 refs)

- 79-5726 Rescue of a Thymotropic, Leukemogenic C-Type Virus from Cultured, Nonproducer Lymphoma Cells of Strain C57BL/Ka Mice. (Eng) Lieberman, M. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Decleve, A.; Ihle, J. N.; Kaplan, H. S. *Virology* 97(1): 12-21; 1979.

The rescue of a thymotropic, leukemogenic C-type virus from a nonproducer cell line by infection with a B-ecotropic, non-thymotropic, nonleukemogenic C57BL/Ka retrovirus, BL/Ka(B), is reported. A permanent cell line, BL/RL₁₂-NP, derived from a radiation-induced C57BL/Ka mouse lymphoid tumor, has remained devoid of murine leukemia virus expression, except for the rare, sporadic initiation of virus production in some cultures. It can, however, be stably infected by radiation leukemia virus (RadLV), and the progeny virus population retains the biological and serological properties of the parental RadLV. The cells can also be infected by the C57BL/Ka virus isolate BL/Ka(B). In the latter situation, the emerging virus particles may exhibit thymotropic and leukemogenic (T+L+) attributes similar to those of RadLV while retaining at least some of the envelope determinants of BL/Ka(B). These observations suggest that, following productive infection by a nonleukemogenic helper virus, oncogenic sequences endogenous to the nonproducer lymphoma cells may be packaged in infectious progeny virions. The data are interpreted as providing strong support for the existence, in radiogenic lymphomas, of defective T+L+ sequences, designated RadLV-O. Possible mechanisms by which RadLV-O is later expressed as an infectious leukemogenic virus are presented. (27 refs)

- 79-5727 Induction of B-tropic and N-tropic Murine Leukemia Virus from B10.BR/SgLi Mouse Embryo Cell Lines by 5-Iodo-2'-deoxyuridine. (Eng) Moll, B. (Dept. Pathology, Lenox Hill Hosp., New York, NY 10021); Hartley, J. W.; Rowe, W. P. *J Natl Cancer Inst* 63(1): 213-217; 1979.

Although there is an excellent correlation between the efficiency with which N-tropic ecotropic murine leukemia virus (MuLV) can be induced by 5-iodo-2'-deoxyuridine (IUdR) or 5-bromodeoxyuridine (BUdR) from mouse embryo cultures and the frequency with which the virus is detectable in adults of the same strains, the correlation between natural occurrence and induction efficiency is not true for B-tropic virus. This study shows that a subline of the B10.BR mouse strain has a high level of B-tropic virus and that embryo cultures from the subline contain IUdR-inducible B- and N-tropic ecotropic MuLV. In contrast to the original B10.BR/SgSn congenic mouse strain, adults of the B10.BR/SgLi subline showed a high level of expression of B-tropic

ecotropic MuLV (94% were virus-positive in one test). Both B- and N-tropic ecotropic MuLV were induced by IUdR in cultures of two virus-free cell lines derived from embryos of B10.BR/SgLi mice, as measured by XC-cell plaque assay of the cell culture medium and subsequent assay of the harvested virus on BALB/c and NIH Swiss embryo cultures. The IUdR-induced virus isolates were similar to prototypic B- and N-tropic ecotropic MuLV in their XC positivity, neutralization pattern, efficient infection of SC-1 and permissive Fv-1-type mouse cells, partial restriction by Fv-1-mb mouse cells, and failure to infect mink lung cells. Of eight additional B10.BR/SgLi cell lines tested, 2 produced B-tropic virus spontaneously, 3 were inducible for both B- and N-tropic viruses, and 3 were inducible for only N-tropic virus. Confirmation that the B-tropic virus of the B10.BR/SgLi cell line is carried as a genetic element was obtained in two ways. First, four clonal lines of an inducible cell line were derived from single cells and four yielded B- and N-tropic virus after IUdR treatment. Second, most of the cultures of F₁ embryos derived from matings of B10.BR/SgLi males with NFS/N or A/J females were inducible for both B- and N-tropic viruses, whereas no ecotropic virus was induced from the NFS/N strain, and only rarely was N-tropic virus induced from the A/J strain. Thus, the information for B-tropic MuLV as well as that for N-tropic MuLV was transmitted as a genetic element in the B10.BR/SgLi subline. (28 refs)

- 79-5728 Biological Characterization of a Leukemogenic Virus Isolated from the CFW Mouse. (Eng) Ball, J. K. (Cancer Res. Lab., Univ. Western Ontario, London, Ontario N6A 5B7, Canada); McCarter, J. A. *Cancer Res* 39(8): 3080-3088; 1979.

Extracts of thymic lymphomas induced in CFW/D mice by dimethylbenz(a)anthracene (DMBA) are leukemogenic when injected into intrarenal thymic grafts. Tumor cell lines established in vitro from tumors induced by these extracts release a C-type virus. This tissue culture (TC)-derived virus (TC-DMBALV: virus produced by TC cell lines established from tumors induced by cell-free tumor extracts or TC cell supernatants) is highly leukemogenic (minimum infectious titer of 1.6×10^6 IU/ml) when injected into 24-hr-old thymus grafts placed under the kidney capsules of normal 6-wk-old adults. The latent period (time in days to tumor detection in 50% of the injected grafts using undiluted TC virus preparations) is very short (30 days postinjection). Thymic lymphomas induced by virus isolated from DMBA-induced tumor virus cells and by TC-DMBALV have been characterized as T-cell thymomas. Productive infection with either of the viral isolates could not be initiated on any of a wide variety of TC cell lines under conditions that readily permitted the recovery of xenotropic and ecotropic C-type viruses in control experiments. The data indicate that, unlike radiation leukemia virus, (1) TC-DMBALV does not infect cell lines in culture and (2) virus isolated from DMBA-induced tumor virus cells does not appear to be accompanied by detectable and/or recoverable levels of xenotropic or ecotropic C-type viruses. TC-DMBALV has a buoyant density and RNA genome characteristic of C-type particles. Polyacrylamide-sodium dodecyl sulfate gel analysis of the viral proteins indicated a markedly altered pattern of gag-coded proteins compared with those of the xenotropic virus induced from a lymphoid-derived cell line established from CFW/D mice. (41 refs)

- 79-5729 A Murine Sarcoma Virus-associated Protein Kinase: Interaction with Actin and Microtubular Protein.

(Eng) Sen, A. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20205); Todaro, G. J. *Cell* 17(2): 347-356; 1979.

A low mol-wt (approx 15K) protein phosphokinase enzyme that binds to actin was isolated from the m3 variant of murine sarcoma virus produced, with a helper murine leukemia virus, by 3B11C mouse 3T3 cells. The kinase activity was not detected in the helper virus preparations. It was purified by Sephadex G-75 gel filtration and affinity chromatography on actin-Sepharose conjugates. In assays using phospho-vin as an exogenous substrate, the enzyme was released from the virions at Triton X-100 concentrations >0.12%. The kinase was inhibited by Triton at concentrations >0.01%, which indicates that it is an internal protein packaged in the virion particles. Only 10%-15% of a high mol-wt (approx 40K) kinase bound to the actin-Sepharose conjugate, but almost 90% of the low mol-wt enzyme was recovered from the actin-bound kinase preparation. The binding of actin molecules to the enzyme was accompanied by inhibition of phosphorylation reactions catalyzed by the enzyme in the presence of actin. The actin-binding enzyme showed a lower but detectable binding to microtubular proteins, and it inhibited the in vitro polymerization of tubulin. This study represents the first isolation of a sarcoma virus-associated protein with the ability to interact directly with two major components of the cytoskeletal system. (42 refs)

79-5730 Composition, Arrangement and Cleavage of the Mouse Mammary Tumor Virus Polyprotein Precursor Pr77^{gag} and p110^{gag}. (Eng) Dickson, C. (Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Atterwill, M. *Cell* 17(4): 1003-1012; 1979.

The [¹⁴C]lysine- and [¹⁴C]arginine-labeled tryptic peptide maps of the nonglycosylated structural proteins of murine mammary tumor virus, the putative *gag* gene-related precursors Pr77^{gag} and p110^{gag}, and the cleavage intermediates derived from Pr77^{gag} were determined. The proteins were labeled with [¹⁴C]lysine and [¹⁴C]arginine so that all but one of the tryptic peptides released from a protein could be detected. As judged from the peptide maps, Pr77^{gag} contained the complete sequences of the four major internal proteins of the virion (p27, pp21, p14 and p10) and possibly a fifth highly basic protein (p8) also found in the virion. The putative cleavage intermediates lacked some tryptic peptides that could be assigned to one or more of the major virion proteins and thus allow a scheme for the cleavage events to be constructed. p110^{gag} contained all tryptic peptides found in Pr77^{gag}, plus some additional peptides. A minor virion protein p30 included the peptides of p14 as well as some of the additional peptides present in p110^{gag} suggesting a precursor-product relationship between the p110^{gag} and p30. The data support the authors' proposal that there are three protein precursors that include, at least in part, the *gag* gene region of the virion -- p160 (potentially a *gag/pol* precursor), p110^{gag} and Pr77^{gag} -- and that the arrangement of the virion proteins within the *gag* gene (pr77 *gag*) is p10-pp21-p27-p14. (63 refs)

79-5731 Mouse Mammary Tumor Cell Surface Antigens. II. Immunogenicity and Expression of MMTV Proteins in the Mouse. (Eng) Fine, D. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD 21701); Arthur, L.; Massey, R.; Schochetman, G. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, R. W., ed. (New York; Elsevier): 590 pp.; 143-168; 1978.

Sera and tissues of mice with different incidences of spontaneous mammary tumors were examined for mouse mammary tumor virus (MMTV) gp52, and the humoral and cellular immunity that occurs against both the virus and the tumor cells was characterized. A specific radioimmunoassay for MMTV gp52 showed that mammary tumor and normal mammary gland tissues from high tumor strains contained 1,500 and 600 nanograms of gp52/mg tissue, respectively. Lymph nodes draining the mammary gland and normal tissues with secretory functions (salivary glands, seminal vesicles, and coagulating glands) also contained gp52. Male and female mice of strains expressing MMTV gp52 and having moderate to high incidences of mammary tumors had antibodies that specifically precipitated MMTV, whereas no antibody was detected in strains with low mammary tumor incidences. Reactivity of natural sera for MMTV showed competition with purified MMTV gp52. High-titered precipitating sera from BALB/c NIV and feral mice specifically precipitated purified MMTV gp52. Gp36 was also immunogenic, because strains of mice with low to moderate tumor incidences developed precipitating antibodies to gp36 and gp52 when inoculated with purified MMTV. Natural sera as well as sera from MMTV-inoculated mice with MMTV precipitating antibody were also cytotoxic for mammary tumor cells in a complement-dependent assay. These sera were specific for cells expressing MMTV antigens, and the development of both precipitating and cytotoxic antibodies was age-dependent. An age-dependent blastogenic response that recognized MMTV and murine leukemia virus and the purified major glycoproteins of the two viruses was found in these same strains of mice. Thus, the development of both humoral and cell-mediated immune responses in the C3Hf mouse demonstrates the ability of the host to recognize endogenous MMTV. (20 refs)

79-5732 Acceleration of Mammary Cancer Development by Grafting of Fetal Mammary Mesenchymes in C3H Mice. (Eng) Sakakura, T. (Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Kanokoden, Tashiro-cho, Chikusa-ku, Nagoya 464, Japan); Sakagami, Y.; Nishizuka, Y. *Gann* 70(4): 459-466; 1979.

Mammary epithelial hyperplasia was induced in 9-wk-old, syngeneic, female C3H/HeN mice, which are carriers of milk-transmitted virulent virus (MTV-S), and in C3H/fHeN mice, which do not carry the virus. Transplantation of fetal mammary gland mesenchyme into the mammary glands of both strains resulted in focal reenactment of events that normally occur during fetal and early postnatal development of the mammary gland. The portions of the recipient's mammary duct system in contact with the fetal mammary mesenchyme underwent branching and proliferation in a pattern resembling that of rudimentary mammary gland development. In mice carrying MTV-S, mammary cancers of Types A and B appeared earlier and more frequently in the mammary glands that had received transplants of fetal mammary mesenchyme, compared with those in the glands that received no fetal mesenchyme. Some of the smaller cancers were shown to develop directly from portions of the mammary gland interacting with fetal mammary mesenchyme, without prior formation of typical hyperplastic alveolar nodules. Cancers did not appear in similarly treated mammary glands of C3H mice not carrying MTV-S. The results suggest that nonhormonal, and probably non-viral factors that stimulate focal proliferation in the mammary duct system as a result of fetal mesenchyme transplantation accelerate local development of mammary cancers. (15 refs)

79-5733 Diversity of Mammary Tumor Viral Genes Within the Genus *Mus*, the species *Mus musculus*, and the strain

C3H. (Eng) Drohan, W. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20205); Schlom, J. *J Virol* 31(1): 53-62; 1979.

Proviral sequences related, or identical, to tumor-associated (TA)-sequence RNA are found in the DNA's of spontaneous mammary tumors that arise early in the life of several high-tumor-incidence mouse strains. These sequences are absent in the DNA's of mammary tumors that occur later in the life of low- and moderate-incidence strains, as well as in apparently normal tissues of a variety of inbred mouse strains, feral mice, and other species and subspecies of *Mus*. Sequences represented in TA sequence RNA, however, are present as endogenous provirus in GR mice (at approx 4 copies per haploid genome) and in 2/5 substrains of C3H mice tested (at approx 1 copy per haploid genome). The two substrains of C3H mice positive for endogenous TA sequence provirus were recently (around 1930) separated from the negative substrains of C3H mice. The results may be explained by the unlikely chance segregation of proviral sequences or by the recent integration of viral genes (within the last few decades). Whereas radioactively labeled mouse mammary tumor virus 60S-70S RNA or complementary DNA detected mouse mammary tumor virus-related proviral information in all laboratory mouse strains, feral mice, subspecies of *M. musculus*, and other species of *Mus*, the use of TA sequence RNA clearly revealed the genetic diversity that may exist between different colonies or substrains of "inbred" laboratory mice commonly used in cancer research. (38 refs)

79-5734 Induction of Mouse Mammary Tumor Virus RNA in Mammary Tumors of BALB/c Mice Treated with Urethane, X-Irradiation, and Hormones. (Eng) Michalides, R. (Div. Virology, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., 1066 CX Amsterdam, Netherlands); van Deemter, L.; Nusse, R.; Hageman, P. *J Virol* 31(1): 63-72; 1979.

The involvement of mouse mammary tumor virus (MTV) in the development of mammary tumors of nonviral etiology in BALB/c mice was studied by measuring the levels of MTV RNA, MTV DNA, and MTV proteins in spontaneously arising and hormonally, chemically, and/or physically induced mammary tumors of BALB/c females. Spontaneous mammary tumors contained very low levels of MTV RNA; $4 \times 10^{-6}\%$ of the cytoplasmic RNA was MTV RNA. No MTV proteins could be demonstrated by using sensitive radioimmunoassays for MTV proteins p27 and gp52. Mammary tumors induced by treatments with urethane or x-rays alone contained higher levels of MTV RNA; these tumors contained 3- and 19-fold more MTV RNA, respectively, compared with spontaneous mammary tumors. Mammary tumors induced by combined treatment with urethane and x-rays expressed high levels of MTV RNA in the mammary tumors; a 1,724-fold increase in MTV RNA content compared with spontaneous mammary tumors was observed. However, very low levels of MTV proteins gp52 and p27 were detected, suggesting some kind of impairment at translation of the MTV RNA. MTV RNA was also induced by this treatment in mammary glands and spleens, but not in the livers of tumor-bearing animals. BALB/c females continuously exposed to prolactin contained high levels of MTV RNA and MTV proteins in stimulated mammary glands and in the hormonally induced mammary tumors. These findings suggest that MTV is not responsible for the maintenance and probably also not for the development of all murine mammary cancers. (30 refs)

and Murine Leukemia Virus (MuLV) Surface-associated Antigens. (Eng) Schochetman, G. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD 21701); Arthur, L. O.; Fine, D. L.; Massey, R. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, R. W., ed. (New York; Elsevier): 590 pp.; 115-141; 1978.

The intracellular regulation and synthesis of mouse mammary tumor virus (MMTV) components were studied, and virus-specific cell-surface antigens (CSA) were identified as potential targets for immune surveillance by the mouse. Labeled viral antigens were analyzed by immunoprecipitation with monospecific antisera directed against MMTV and murine leukemia virus (MuLV) proteins followed by gel electrophoresis. On cultured virus- and non-virus-producing cells, both MMTV gp52 and MuLV gp70 were iodinated, even though the gp52 precursor polyprotein (gPr75 - MMTV env) was readily isolated from the cells. In addition, gp52 and gp70 were iodinated on primary mammary tumor cells never placed in culture, whereas only gp70 was iodinated on lymphocytes from the same tumor-bearing animal. Cultured tumor cells that simultaneously produced MMTV and MuLV also contained a possible precursor to gp70 and two CSA of 85,000 and 95,000 daltons that were analogous to the Gross CSA (GCSA). Extracellular MMTV and MuLV from these cells contained only labeled gp52 and gp70, respectively, indicating that these two viral envelope glycoproteins are present on mutually exclusive viral budding sites that are distinct from the surface sites occupied by GCSA. The galactose oxidase labeling method also demonstrated the cell-surface locations of gp52, gp70, and the possible gp70 precursor. However, this method also labeled MMTV gp36, indicating that at least its carbohydrate regions are exposed. These results demonstrate that gPr75 is cleaved prior to the appearance of gp52 on the cell surface and that gp52, gp70, and, possibly, gp36 are tumor CSA and potential targets for the immune response in mice. (25 refs)

79-5736 Effect of Parity Regimen on the Rate of Occurrence of Mammary Tumors in A, C3H, and RIII Mice. (Eng) Moore, D. H. (Dept. Microbiology and Immunology, Hahnemann Medical Coll. and Hosp., Philadelphia, PA 19102); Holben, J. A. *Int J Cancer* 24(2): 161-164; 1979.

The effect of breeding regimen (early in life, late, continuous, or not at all) on the incidence of mammary tumors was studied in A, RIII, and C3H mice. The response to the breeding regimen was different in each of the three strains. The C3H stock was affected least, although the tumor occurrence rate was slower in virgins. In both A and RIII, only one litter at puberty resulted in the tumors occurring over the greatest age range; in RIII mice, the occurrence rate and the mean tumor age were similar to those of virgins. Normal continuous breeding caused the earliest tumors in all three strains, although in RIII mice, breeding after 18 wk of age also caused very early tumors. The response of the RIII strain to parity variations was more like that of humans than was the response of either of the other strains. Removal of the milk-transmitted virus from these strains by foster-nursing resulted in vastly different mammary tumor occurrence rates, the quantitative changes being different in each mouse strain. (18 refs)

79-5735 Mouse Mammary Tumor Cell Surface Antigens (CSA). I. Mouse Mammary Tumor Virus (MMTV)

79-5737 Virus Production by Abelson Murine Leukemia Virus-transformed Lymphoid Cells. (Eng) Shields, A. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA

02139); Rosenberg, N.; Baltimore, D. *J Virol* 31(2): 557-567; 1979.

A systematic investigation was made of virus production by Abelson murine leukemia virus (A-MuLV)-transformed cells. Lymphoid cell lines obtained by in vitro transformation of NIH/Swiss bone marrow cells with A-MuLV can be divided into three classes: producers releasing reverse transcriptase (RT)-containing particles and infectious virus; nonproducers releasing no viral particles; and defective producers, the most common phenotype, releasing particulate RT in the absence of infectious virus. When these cell lines were analyzed 1-2 wk after their isolation, however, all produced infectious virus. Because these cell lines were carried in culture, many ceased to release infectious virus but produced defective virions. One defective producer, SWR4, was studied extensively. The particles it produces have the same density as that of virions of Moloney murine leukemia virus (M-MuLV). The particles contain no 35S-70S RNA, as determined by analysis of [³H]uridine-labeled particles, and they exhibit no endogenous RT activity. Although the RT enzyme is of normal size, the major structural protein of the defective virions has a mol wt of 28,000 (p28), in contrast to the p30 of M-MuLV, and no viral glycoprotein is evident. The defective particles do not appear to arise either from the helper virus or from Abelson virus. An alteration of the protein of the helper virus is an unlikely source of p28, because particles produced by lymphoid cells transformed with another strain of M-MuLV as helper (M-MuLV-TB) contained p28 with an unaltered cleavage pattern, although M-MuLV-TB p30 differs from M-MuLV p30. The A-MuLV genome lacks the capacity to code for the RT and p28 of the defective virions and, therefore, cannot be the source of the defective virions. Clones of fibroblasts infected with A-MuLV only occasionally produce defective particles. The defective particles therefore probably arose from an endogenous virus that is preferentially expressed in the class of lymphoid cells transformed by A-MuLV. This interpretation implies that most of A-MuLV-transformed lymphoid cells completely lose expression of the helper virus genome. (35 refs)

79-5738 Phenotypic Mixing Between Murine Oncoviruses and Murine Cytomegalovirus. (Eng) Schnitzer, T. J. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Gonczol, E. *J Gen Virol* 43(3): 691-695; 1979.

In vitro interactions between murine cytomegalovirus (MCMV) and murine leukemia viruses (MuLV's), two groups of enveloped viruses capable of causing persistent or latent infections in vivo, were examined for evidence of phenotypic mixing, since pseudotype formation could alter the spread of these viruses and be important in their pathogenesis. The growth of MCMV in murine cells productively infected with ecotropic MuLV resulted in the production of phenotypically mixed particles having the envelope antigens of MuLV and the genome of MCMV [MCMV(MuLV) pseudotypes]. The identity of these pseudotype particles was confirmed by the use of specific anti-MuLV serum and by the demonstration of restriction, due to viral interference, of the penetration of these particles on MuLV-infected murine cells. This restriction was independent of N- or B-tropism. The production of reverse pseudotypes could not be examined because of the lytic effects of MCMV on the requisite assay cells. (28 refs)

79-5739 Identification of Proteins Specific to Friend Strain of Spleen Focus Forming Virus (SFFV). (Eng) Ikawa, Y.

(Dept. Viral Oncology, Cancer Inst., Tokyo, Japan); Yoshida, M.; Yoshikura, H. *Proc Japan Acad, Ser B: Phys Biol Sci* 54(10): 651-656; 1978.

The identification of 55,000- and 120,000-dalton proteins as spleen focus-forming virus (SFFV)-specific proteins is described. The former cross-reacted with anti-Rauscher murine leukemia virus gp70 serum and was abundant in SFFV-producing and nonproducing SFFV-infected erythroleukemia clones. A large quantity of the other protein was detected in SFFV-infected normal rat kidney cells. These proteins are probably coded for by the SFFV genome. (20 refs)

79-5740 Spleen Focus-forming Friend Virus: Identification of Genomic RNA and Its Relationship to Helper Virus RNA. (Eng) Evans, L. H. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Duesberg, P. H.; Troxler, D. H.; Scolnick, E. M. *J Virol* 31(1): 133-146; 1979.

The genome of the defective, murine spleen focus-forming Friend virus (SFFV) was identified as a 50S RNA complex consisting of 32S RNA monomers. Electrophoretic mobility and the mol wt of unique RNase T₁-resistant oligonucleotides (T₁-oligonucleotides) indicated that the 32S RNA had a complexity of about 7.4 kilobases. Hybridization with DNA complementary to Friend murine leukemia virus (Fr-MLV) distinguished two sets of nucleotide sequences in 32S SFFV RNA, 74% which were Fr-MLV related and 26% which were SFFV specific. By the same method, SFFV RNA was 48% related to Moloney MLV. A total of 23 large T₁-oligonucleotides of SFFV and 43 of Fr-MLV RNA's, were resolved. The former were classified as follows on the basis of the relationship between the SFFV and Fr-MLV RNA's: (1) seven which had homologous equivalents in Fr-MLV RNA; (2) six more which could be isolated from SFFV RNA-Fr-MLV complementary DNA hybrids treated with RNases A and T₁; (3) eight more which were isolated from hybrids treated with RNases T₁; and (4) two which did not have Fr-MLV-related counterparts. Surprisingly, the two class 4 oligonucleotides had homologous counterparts in the RNA of six amphotropic MLVs including mink cell focus-forming and HIX-MLVs analyzed previously. The map locations of the 23 SFFV T₁-oligonucleotides relative to the 3' polyadenylic acid coordinate of SFFV RNA were deduced from the size of the smallest polyadenylic acid-tagged RNA fragment from which a given oligonucleotide was isolated. The resulting oligonucleotide map could be divided roughly into three segments: two terminal segments which are mosaics of oligonucleotides of classes 1, 2, and 3, and an internal segment between 2 and 2.5 kilobases from the 3' end containing the two oligonucleotides shared with amphotropic MLVs. Since SFFV RNA consists predominantly of sequence elements related to ecotropic and amphotropic helper-independent MLVs, it would appear that the transforming gene of SFFV is not a major specific sequence unrelated to genes of helper viruses, as is the case with Rous sarcoma and probably with other defective sarcoma and acute leukemia viruses. (53 refs)

79-5741 Pluripotential Stem Cell Replication in Continuous Human, Prosimian, and Murine Bone Marrow Culture. (Eng) Moore, M. A. (Labs. Developmental Hematopoiesis, Sloan Kettering Inst. Cancer Res., 1250 First Ave., New York, NY 10021); Sheridan, A. P. *Blood Cells* 5(2): 297-311; 1979.

The capacity of Friend leukemia virus to transform pluripotential

stem cells (CFU-s) or committed progenitor cells in continuous marrow cultures was studied using a cloned stock of Friend helper C-type virus (F-MuLV) or spleen focus-forming virus (SFFV) isolated free of replicating helper virus in nonproducer fibroblast lines. Marrow cultures infected with F-MuLV in the absence of SFFV began to deviate from normal by 10-11 wk. The deviation was marked by a stabilization and then increase in cell production with an increasing predominance of immature granulocytic elements and granulocyte-macrophage progenitors (CFU-c). At 15 wk, a marked increase in the cloning efficiency of the F-MuLV-infected cultures was associated with the predominance of small, tight, cerebrospinal fluid (CSF)-dependent colonies composed of maturing granulocytes. Cultures infected with SFFV plus F-MuLV did not exhibit the phenotypic changes seen in the F-MuLV-infected cultures. Significant changes in hematopoiesis were seen within 3 wk of infection of the cells with the Kirsten murine sarcoma virus pseudotype. These involved conversion to a predominantly macrophage morphology with drastic declines in CFU-c and CFU-s. In human bone marrow cultures, there was a sustained replication of CFU-c and production of myeloid cells for several weeks; colony size, morphology, and CSF responsiveness were indistinguishable from those of normal cultures. The *Tupaia*, one of the most primitive living prosimians, is hematologically very similar to humans, but an adherent marrow environment established from this species was similar to that seen in the mouse. (16 refs)

- 79-5742 Group-specific Cytolytic Antibody Directed Against the Major Glycoprotein (gp70) of Murine Leukemia Viruses in Serum of Mice with Dormant FLV Infections. (Eng) Callahan, R. M. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA 19107); Marx, P. A.; Wheelock, E. F. *Virology* 97(1): 55-67; 1979.

The antibody in Friend leukemia virus (FLV) immune serum (FVIS) that is responsible for the lysis of Friend erythroleukemia (FLC-745) cells was studied. Gp70 was the only FLV antigen on the FLC-745 cells that was able to be a target for cytolysis by virus-specific antibody, and a nonvirion FLV cellular antigen was excluded as a target for FVIS cytolytic activity. Determination of the group specificity of the cytolytic activity of serum from mice with dormant FLV infections indicated that a group-specific gp70 antibody in FVIS was responsible for FLC-745 cell lysis and distinguished FVIS from Friend/Moloney/Rauscher murine leukemia virus-specific cytolytic antibody. Competition radioimmunoassay with FLV, AKR, and feline leukemia viruses indicated that FVIS must contain type-specific gp70 antibody in addition to a group-specific cytolytic antibody. However, this type-specific antibody was not cytolytic for FLC-745 cells, since AKR virus was able to block cytolysis completely. The data suggest that the cytolytic antibody in FVIS is directed against gp70, and they suggest that this antibody is involved in the suppression of FLV to a dormant state. (37 refs)

- 79-5743 Anti-Friend Virus Antibody Is Associated with Recovery from Viremia and Loss of Viral Leukemia Cell-Surface Antigens in Leukemic Mice. Identification of Rfv-3 as a Gene Locus Influencing Antibody Production. (Eng) Doig, D. (Rocky Mountain Lab., Natl. Inst. Allergy and Infectious Diseases, NIH, Hamilton MT)(59840); Chesebro, B. *J Exp Med* 150(1): 10-19; 1979.

The mechanism of action of the non-H-2 gene Rfv-3 was studied in

several mouse strains. Rfv-3 influenced Friend virus (FV) viremia, loss of FV-induced cell-surface antigens from leukemia cells, and generation of anti-FV antibodies. At 30-90 days after FV infection, leukemic spleen cells from (B10.A x A)F₁ and (B10.A x A.BY)F₁ mice (Rfv-3 r/s) had low FV-induced cell-surface antigen expression compared with leukemic spleen cells from A and A.BY mice (Rfv-3^{+/+}). In addition, these F₁ mice recovered from viremia and generated cytotoxic anti-FV antibodies. A and A.BY mice did not recover from viremia and they failed to generate anti-FV antibodies. Anti-FV leukemia cell antibody appeared to mediate FV-antigen loss, because a decrease of FV cell-surface antigens occurred at the same time as anti-FV antibody appeared in the plasma of F₁ mice, and passive transfer of anti-FV antisera induced modulation of FV cell-surface antigens. Rfv-3 did not influence an intrinsic ability of FV antigens to be modulated from Rfv-3^{+/+} leukemia cells, because FV antigen loss from Rfv-3^{+/+} spleen cells occurred after the cells were transferred to an immune environment. (28 refs)

- 79-5744 The Generation and Specificity of Cytotoxic T Cells Raised Against Syngeneic Tumor Cells Bearing AKR/Gross Murine Leukemia Virus Antigens. (Eng) Green, W. R. (Basic Immunology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Nowinski, R. C.; Henney, C. S. *J Exp Med* 150(1): 51-66; 1979.

Experiments aimed at determining whether the ability to generate cytotoxic activity against syngeneic gross cell-surface antigen-positive tumors correlates with Rgv-directed resistance to leukemogenesis were performed. Rgv is a locus mapping in the region that controls immune responsiveness. Efforts were made to generate C57BL/6 cytotoxic effector cells to a syngeneic leukemia (E male G2) bearing AKR/Gross virus antigens (GVA). No significant cytotoxicity was induced by immunization with up to 10⁸ irradiated E male G2 cells, even when cells from such primed animals were subsequently restimulated with E male G2 cells in vitro. Consequently, C57BL/6 mice were immunized with an allogeneic, virus-producing AKR leukemia cell line (AKR SL3). Peritoneal exudate cells and, to a lesser degree, spleen cells from these mice showed significant lytic activity toward the immunizing allogeneic tumor but not toward E male G2. When spleen cells were harvested from animals approx 10 days after injection of AKR SL3 and rechallenged in vitro with either E male G2 or AKR.H-2b SL1, another tumor that displays AKR/GVA, a vigorous cytotoxic response against E male G2 and AKR.H-2b was obtained. Effector cells generated by AKR SL3 priming followed by in vitro stimulation with E male G2 or AKR H.2b SL1 lysed only cells of the H-2b haplotype that were strongly positive for the display of serologically detectable AKR/GVA. Thus, AKR SL3 cells were not lysed nor were EL4 cells (H-2b, but only weakly positive for gp70). Cells not bearing the murine leukemia virus antigens tested for, such as P815 mastocytoma cells and spleen cell "blasts" from C57BL/6 and CBA (H-2k) mice, were also not susceptible to attack. The cytotoxic effector cells induced bore Thy 1.2 alloantigen and were of the Lyt 1 + 2 + phenotype. Collectively, these findings are consistent with the conclusion that the cytotoxic T cells raised against E male G2 are directed against GVA and are H-2-restricted. (33 refs)

- 79-5745 Loss of Proviral DNA Sequences in a Revertant of Kirsten Sarcoma Virus-transformed Murine Fibroblasts. (Eng) Trainor, C. D. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD 20014); Reitz, M. S. *J Gen Virol* 44(1): 245-249; 1979.

The revertant cell line (K-BALB SR¹²¹²), derived as a single cell clone from a clonal line of murine fibroblasts (K-BALB) transformed by nonproductive infection with Kirsten murine sarcoma virus (Ki-MSV), has normal morphology and growth kinetics and, unlike the transformed parent cell line, lacks a rescuable sarcoma virus. This reversion was found to correlate with low to undetectable levels of expression of cellular Ki-MSV-specific RNA and a reduction of proviral sequences in the cell DNA to a level equivalent to that found in the uninfected BALB cells with a normal phenotype. The data indicate that phenotypic reversion has occurred as a consequence of the loss of part or all of the sarcoma provirus, either by chromosome rearrangement or provirus excision. (19 refs)

- 79-5746 Cycloheximide-dependent Reversion of Human Cells Transformed by MSV and Chemical Carcinogen. (Eng) Cho, H. Y. (Dept. Experimental Pathology, Walter Reed Army Inst. Res., Washington, DC 20012); Rhim, J. S. *Science* 205(4407): 691-693; 1979.

Evidence is presented that morphologic reversion and selective inhibition of growth can be observed in virally or chemically transformed human cells after treatment with protein synthesis inhibitor cycloheximide (CH). CH, at a concentration of 0.08 $\mu\text{g}/\text{ml}$, induced a flat morphology within 24-48 hr and a low saturation density in human osteosarcoma cells transformed by Kirsten murine sarcoma virus or N-methyl-N'-nitro-N-nitrosoguanidine. Removal of CH caused both transformed cells to revert to the transformed phenotype. The demonstration of cell-surface antigens, cross-reacted with antisera induced by extracts of both types of transformed human cells, was dependent on the presence or absence of CH in the culture medium. The results show that protein synthesis is required to maintain the transformed state in virally or chemically transformed human cells. (20 refs)

- 79-5747 Effects of Protease Inhibitors on Chemical Induction of Type C Virus. (Eng) Long, C. W. (Frederick Cancer Res. Center, P.O. Box B, Building 560, Frederick, MD 21701); Bruszewski, J. A.; Christensen, W. L.; Suk, W. A. *Cancer Res* 39(8): 2995-2999; 1979.

The effects of protease inhibitors on the chemical induction of endogenous xenotropic C-type virus from Kirsten sarcoma virus-transformed BALB/c 3T3 mouse cells was examined. Two distinct classes of protease inhibitors, the trypsin inhibitor α -N-tosyl-L-lysine chloromethyl ketone and two naturally occurring oligopeptide inhibitors, antipain and leupeptin, were found to inhibit induction of virus by cycloheximide and histidinol. Virus activation by 5-iododeoxyuridine was inhibited to a lesser degree. During the time cells were exposed to these compounds, there was little inhibition of [³H]uridine incorporation into total cellular RNA or polyadenylic acid-containing cytoplasmic messenger RNA, suggesting that inhibition of proteolysis, and not RNA transcription, was responsible for blocking virus induction. (41 refs)

- 79-5748 Decrease in Epidermal Growth Factor Receptor Levels and Production of Material Enhancing Epidermal Growth Factor Binding Accompany the Temperature-dependent Changes from Normal to Transformed Phenotype. (Eng) Guinivan, P. (Div. Genetics, Dept. Pediatrics, Coll.

Medicine, Pennsylvania State Univ., Hershey, PA 17033); Ladda, R. L. *Proc Natl Acad Sci USA* 76(7): 3377-3381; 1979.

The growth-promoting activity and binding characteristics of epidermal growth factor (EGF) on normal rat kidney (NRK) cells and derivatives of these cells transformed by Kirsten murine sarcoma virus (KNRK cells) and a temperature-sensitive mutant of the virus (Ts cells) were investigated. The Ts cells exhibited a normal monolayer morphology identical to that observed for uninfected NRK cells at the nonpermissive temperature (39 C), but they grew as multilayered foci resembling KNRK cells at the permissive temperature (32 C). NRK cell division was stimulated by EGF, and these cells showed high levels of EGF receptors, as determined by ¹²⁵I-labeled EGF binding. KNRK cells were unresponsive to EGF, and no EGF receptors were detectable. Ts cells also were unresponsive to EGF at both temperatures, but they exhibited just-detectable EGF binding at 32 C and 10%-15% of NRK cell binding at 39 C. Use of EGF added to the culture medium by these cells paralleled the receptor levels. Cross-feeding experiments among NRK, KNRK, and Ts cultures indicated that Ts cells at the permissive temperature and KNRK cells at both temperatures produced a heat-stable substance(s) that stimulated DNA synthesis in NRK cells independent of the presence of serum or EGF. Conditioned medium from the transformed cultures also significantly enhanced EGF binding to NRK cells. These studies demonstrated a correlation between the transformed phenotype and the receptor levels of a potent cell mitogen, EGF, which was readily reversible in the Ts cultures. In addition, cultures expressing the transformed phenotype produced material that did not compete for the EGF receptor but did enhance EGF binding, in contrast to other reports involving sarcoma virus-transformed cells. (25 refs)

- 79-5749 Different Rat-derived Transforming Retroviruses Code for an Immunologically Related Intracellular Phosphoprotein. (Eng) Young, H. A. (Lab. Tumor Virus Genetics, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20205); Shih, T. Y.; Scolnick, E. M.; Rasheed, S.; Gardner, M. B. *Proc Natl Acad Sci USA* 76(7): 3523-3527; 1979.

Three distinct fibroblast-transforming retroviruses were isolated from rats. Two of these viruses, Kirsten murine sarcoma virus (Ki-MSV) and Harvey murine sarcoma virus (Ha-MSV), were isolated by experimental inoculation of mouse C-type viruses into rats. The third virus, rat sarcoma virus (RaSV), was isolated in cell culture by cocultivation of a cell producing rat C-type viruses and a Fischer rat cell transformed by 4-nitroquinoline. These three retroviruses code for a related intracellular phosphoprotein that is not a virion structural protein. Ki-MSV and Ha-MSV code for a phosphoprotein, p21. p21 was identified with antisera prepared by transplantation in rats of syngeneic Ha-MSV- or Ki-MSV-transformed nonproducer cells. RaSV apparently codes for the phosphoprotein p29, which shares immunological determinants and common V-8 protease-generated peptides with the p21 of Ha-MSV. The data suggest that RaSV has acquired genetic information with similar coding capacity to some rat genetic information in the mouse-rat recombinant viruses Ki-MSV and Ha-MSV. Based on data obtained for the p21 of a mutant of Ki-MSV temperature-sensitive for the maintenance of transformation, it is suggested that the gene in RaSV that codes for p29 is also required for the maintenance of RaSV-induced fibroblast transformation. (28 refs)

- 79-5750 Presence of Virus-specific DNA Sequences in Murine Type C Viruses. (Eng) Byers, M. J. (La Jolla Cancer

Res. Foundation, Box 1376, La Jolla, CA); Avery, R. J.; Boaz, J.; Kohne, D. E. *J Gen Virol* 43(3): 611-621; 1979.

Total nucleic acids prepared from the Moloney and Rauscher leukemia viruses and the Kirsten leukemia/sarcoma virus complex were found to contain virus-specific DNA (vsDNA) in addition to genomic RNA. This vsDNA was at least partially double-stranded, and it was present within the virus core particle. Data obtained from studies of the extent of hybridization, hybridization kinetics, and thermal stability indicated that the DNA isolated from the virus was greatly enriched in vsDNA relative to that from virus-infected cells. Radioactive complementary DNA (cDNA) produced by the endogenous virus reverse transcriptase was used to detect these vsDNA sequences. In several cases, the cDNA preparations were reacted with purified virus RNA at low RNA:DNA ratios, and the hybridizing fraction was used to detect vsDNA. This selected cDNA reacted $\geq 85\%$ with homologous virus RNA with the kinetics of hybridization expected for a virus RNA:cDNA reaction of c-type RNA complexity. Thus, it is highly unlikely that the cDNA reacting with the virion DNA represented anything but vsDNA. The different cDNA's reacted 20%-60% with their respective virion DNA preparations. The reason for the considerable variation in the extent of reaction of the cDNA with the virion DNA is not known. It is possible that each different extent of reaction is a consistent feature of each different virus type. The origin of the vsDNA present in virion DNA is not known. Proviral DNA sequences may somehow be preferentially included in the virus during assembly of the virus in the cell. Alternatively, the vsDNA may be synthesized after virus assembly by the action of reverse transcriptase on the virion RNA. The biological role of vsDNA is not known, but an interesting speculation is that it is somehow involved in cell transformation. (18 refs)

79-5751 Purification of Protein Kinase of Mouse Sarcoma Virus and Its Effect on Reverse Transcriptase Activity. (Eng) Rokutanda, M. (Dept. Biochemistry, Tokyo Metropolitan Inst. Medical Science, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113, Japan); Maeda, Y. Y.; Takahama, S. *Biochem Biophys Res Commun* 88(4): 1322-1328; 1979.

A protein kinase associated with purified virions of Moloney sarcoma virus (MSV) was purified by ion-exchange chromatography and separated from reverse transcriptase by poly A-Sepharose column chromatography. The reverse transcriptase of MSV was activated 1.6- to 3.5-fold upon incubation with ATP and protein kinase. The reverse transcriptase was activated by protein kinase as a result of phosphorylation, as confirmed by polyacrylamide gel electrophoresis. It is suggested that phosphorylation is one of the mechanisms that regulates the reverse transcriptase activity of MSV. (9 refs)

79-5752 RNA-directed DNA Synthesis in Moloney Murine Leukemia Virus: Interaction Between the Primer tRNA and the Genome RNA. (Eng) Peters, G. (Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2A 3PX, England); Dahlberg, J. E. *J Virol* 31(2): 398-407; 1979.

The interaction between transfer RNA^{Pro} (tRNA^{Pro}) and Moloney murine leukemia virus (M-MuLV) genome RNA was examined. Initiation of RNA-directed DNA synthesis in virions of M-MuLV required a cellular tRNA^{Pro} as primer. The site(s) on the M-MuLV genome RNA at which functional primer molecules were bound and at which purified tRNA^{Pro} hybridized was located near (within

20%) the 5' end of the genome. A relatively stable duplex (50% dissociation occurred at 76 C) was formed between the amino acid acceptor stem of the tRNA^{Pro} and a complementary sequence in the M-MuLV 35S RNA. The interaction involved 19 base pairs, extending from the penultimate nucleotide at the 3' end of the tRNA^{Pro} but apparently not including the 3'-terminal adenosine residue. In most respects, the interaction between primer and template in M-MuLV paralleled the situation in the avian leukosis-sarcoma viruses. (36 refs)

79-5753 Interactions of Retroviruses with Chemical Carcinogens. I. Noncovalent Binding of Unactivated Polycyclic Aromatic Hydrocarbons. (Eng) Harris, R. M. (Worcester Foundation Experimental Biology, Shrewsbury, MA 01545); Kupfer, D.; Luftige, R. B. *Virology* 97(1): 42-54; 1979.

The noncovalent binding of three carcinogenic polycyclic aromatic hydrocarbons (PAH's), benzo(a)pyrene, 3-methylcholanthrene, and 7,12-dimethylbenz(a)anthracene, to retroviruses (RV's) was quantitated using a rate zonal centrifugation assay, and the effects of the binding on a RV specific function, reverse transcription, were determined. The binding level for the enveloped RV's was much higher than that found for nonenveloped viruses (2.5- to 40-fold greater), such as bacteriophage T4 and adenovirus type 5. There was no special affinity of PAH compounds for RV's, as compared with another enveloped virus, Sindbis virus, and there was no binding to viral glycoproteins (type-specific antigens). These results suggest that the binding is best interpreted as partitioning of the hydrophobic PAH compounds between viral envelope lipids and the surrounding aqueous buffer. This interpretation is supported by the temperature and salt dependence of the binding. Using isolated retroviral cores, it was also found that there is a relatively small, but significant, level of binding of benzo(a)pyrene to retroviral cores. Further, the noncovalent binding of benzo(a)pyrene to Rauscher leukemia virus inhibits the RNA-dependent DNA polymerase activity. The inhibition requires preincubation of the virus and PAH, ie, the formation of noncovalent virus-PAH complexes, and it is consistent with a non-competitive model of enzyme inhibition with an inhibition constant, K_i , of about 40 μM . (34 refs)

79-5754 Radioimmunoassay Determination of Two Main Cross-reacting Viral Antigens During Radiation and Rauscher Induced Leukemias. (Eng) Sassen, A. (Dept. Radiobiology, CENSCK, 2400, Mol, Belgium); Plaetse, F. V.; Janowski, M.; Maisin, J. R. *Biomedicine* 30(3): 147-155; 1979.

The two main cross-reacting viral antigens produced during the evolution of radiation(RadLV)- and Rauscher leukemia virus (RLV)-induced leukemias in rats and mice were studied by radioimmunoassay. The p30 proteins from RLV and an RadLV derived from serial passages in rats [RadLV(rat)] were serologically indistinguishable, and they represented approx 15% of the total viral proteins in both cases. The gp70 proteins from RLV and RadLV(rat) showed partial identity based on competition curves. In C57Bl mice with leukemia induced by x-irradiation or by RadLV derived from serial passages in mice (RadLV-RS), the serum p30 level increased slightly during the course of the two leukemias. Gp70-related antigen (gp70-ra) was present in high concentrations in the serum 2-3 wk after treatment, especially in mice treated with RadLV-RS. In the spleens and lymph nodes of the RadLV-RS mice, the p30 level increased markedly and reached higher levels than did the gp70-ra; the reverse was usually observed

in the spleens and thymuses of RadLV mice. In Balb/c mice inoculated with RLV, the serum p30 level increased in parallel with spleen wt. The gp70 concentration did not show such a rapid increase. During RadLV(rat)-induced leukemia, large amounts of p30 and, to a lesser extent, gp70-ra were found in the tissues. Natural antibodies against the RLV and gp70 antigens were not found. The catabolic degradation of labeled RLV gp70 was similar in normal and leukemic mice. (40 refs)

- 79-5755 Glycopeptides of Murine Leukemia Viruses. I. Comparison of Two Ecotropic Viruses. (Eng) Kemp, M. C. (Dept. Microbiology, Univ. Alabama Medical Center, Birmingham, AL 35294); Basak, S.; Compans, R. W. *J Virol* 31(1): 1-7; 1979.

The glycopeptides obtained by pronase digestion of two ecotropic strains of murine leukemia virus (MuLV) were compared by gel filtration. Four different glycopeptide size classes, designated G₁, G₂, G₃, and G₄ with mol wts of approx 5,100, 2,900, 2,200, and 1,500, respectively, were shown to be associated with Rauscher MuLV virions grown in JLS-V9 cells. Various sugar precursors, including glucosamine, galactose, fucose, and mannose, were incorporated into G₁ and G₂, suggesting that these are complex (type I) glycopeptides. The two smaller glycopeptide size classes, G₃ and G₄, were shown to be mannose-rich (type II) glycopeptides. G₄ was more sensitive to digestion with endo- β -N-acetylglucosaminidase H than G₃, suggesting that the core of G₃ may contain fewer mannose residues. Glycopeptides of the same size class as G₁ and G₂ were associated with both Rauscher MuLV and AKR-MuLV grown in I116A (mouse embryo) cells. Previous studies have shown that gp52, a proteolytic cleavage product of gp70, possesses primarily G₁ glycopolypeptides and that gp52 is more highly sulfated than gp70. G₁ was approx twofold more highly sulfated than G₂; thus the observed difference in sulfation of gp52 is explained. The usually large size of G₁ suggested that infection with MuLV may alter the host cell glycosylation pattern. To test this possibility, glycopeptides from Sindbis virions grown in uninfected and Rauscher MuLV-infected JLS-V9 cells were compared, and no differences were observed. G₁ was not detected in Sindbis virions, indicating that acquisition of G₁ depends on properties of the virus-coded polypeptide backbone of the gp70 molecule. (36 refs)

- 79-5756 Quantitative Changes in Spleen Cellularity in Mice Inoculated with Rauscher Leukemia Virus and *Brucella abortus*. (Rus) Belianchikova, N. I. (Lab. Tumor Virology, Cancer Res. Center, Moscow, USSR); Veskova, T. K.; Chimishkian, K. L.; Trubcheninova, L. P.; Svet-Moldavskii, G. Ia.; Gusovskaia, I. M. *Vopr Onkol* 25(6): 76-80; 1979.

The effect of combined infection with Rauscher leukemia virus (RLV) and *Brucella abortus* (BA) was studied in BALB/c mice. Animals were inoculated with RLV (10³ median infective dose, iv) and, on the next day, with live *Brucella* vaccine (10⁹ microbes in 0.2 ml soln). The mice were sacrificed at various times after infection, and spleen cellularity was determined. The total spleen cellularity in mice exposed to RLV + BA was significantly greater than that in controls infected with RLV alone. The increase was caused by BA-induced proliferation of the lymphoid tissue and by the development of the leukemic process. Administration of BA inhibited the proliferation of leukemic erythroblasts and normalized the count of megakaryocytes and plasma cells. (11 refs)

- 79-5757 Propagation and Characterization of a C-Type Virus from a Rhabdomyosarcoma of a Corn Snake. (Eng) Clark, H. F. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Andersen, P. R.; Lunger, P. D. *J Gen Virol* 43(3): 673-683; 1979.

Electron microscopy previously demonstrated the presence of budding C-type viruses in an embryonic rhabdomyosarcoma of a corn snake (*Elaphe guttata*). More recently, virus [corn snake retrovirus (CSRV)] was recovered from rhabdomyosarcoma tissue suspensions inoculated onto cells of a rattlesnake fibroma cell line or cultures of early passage cells derived from a normal rattlesnake heart or kidney. Attempts to cultivate the virus in other reptilian cell systems were unsuccessful. The virus was classified as a retrovirus on the basis of electron microscope observations of fine structure and morphogenesis and the demonstration of virion-associated reverse transcriptase and a buoyant density of 1.16. Polypeptide analysis of CSRV by polyacrylamide gel electrophoresis revealed the presence of five major polypeptides: three had mobility analogous to that of structural polypeptides of viper retrovirus (VRV), but two polypeptides, one of mol wt approx 16,000 and a glycoprotein of mol wt approx 72,000, were unique. Antigenic comparison of CSRV and VRV by agar gel immunodiffusion revealed that CSRV possesses a major antigenic determinant that is different from that of VRV. CSRV propagated in rattlesnake fibroma cells was slowly cytopathic for rattlesnake heart and kidney cells in vitro. (33 refs)

- 79-5758 Involvement of Different Exogenous Feline Leukemia Virus Subgroups in the Generation of Independent Feline Sarcoma Virus Isolates. (Eng) Robbins, K. C. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD 20014); Barbacid, M.; Porzig, K. J.; Aaronson, S. A. *Virology* 97(1): 1-11; 1979.

Complementary DNA (cDNA) probes synthesized from clonal isolates of three feline leukemia virus (FeLV) subgroups were used to study the genetic relatedness of these subgroups. The extent of cross homology detected between the genomes of the three strains ranged from 78% to 88%. The thermal stabilities of heterologous viral cDNA-RNA hybrids were significantly lower than those of homologous hybrids. None of the FeLV subgroup cDNA's was hybridized >50% by normal cat cellular DNA. The thermal stability values of hybrids formed between FeLV-A, -B, or -C-infected cat cellular DNA and the homologous FeLV viral cDNA were 86.4, 84.9, and 86.4 C, respectively. The data indicate that none of the known FeLV subgroups was fully represented as an endogenous virus of cat cells. The SM isolate of feline sarcoma virus (FeSV) contained a larger fraction of FeLV genetic information than either the GA or ST isolates of FeSV, and the thermal stability data suggested that FeLV-B was the source of the FeLV nucleotide sequences in SM-FeSV. In spite of a very high degree of immunologic relatedness among the respective gag gene-coded p15 and p12 proteins of the FeLV subgroups, type-specific determinants could be detected. The pattern of reactivity of each FeLV variant in a series of p15 typing immunoassays served to distinguish the variants. Data derived from empirically devised FeLV p15 typing assays suggested that a different FeLV was involved in the generation of each of the three known isolates of FeSV. (58 refs)

- 79-5759 Influence of Adrenal Corticosteroids on the Susceptibility of Cats to Feline Leukemia Virus Infection.

(Eng) Rojko, J. L. (Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Road, Columbus, OH 43210); Hoover, E. A.; Mathes, L. E.; Krakowka, S.; Olsen, R. G. *Cancer Res* 39(9): 3789-3791; 1979.

The effect of a synthetic adrenocorticosteroid hormone, methylprednisolone acetate (MPA), on resistance to feline leukemia virus (FeLV) infection and leukemogenesis in adult cats was determined. The natural resistance of adult specific-pathogen-free cats to FeLV was abrogated by treatment of the cats with 5-50 mg/kg MPA im, prior to either po-nasal or ip inoculation of FeLV. Persistent viremia was induced in 18/22 MPA-treated cats vs 1/9 age-matched control cats. MPA-treated FeLV-inoculated cats developed prolonged lymphopenia (2-8 wk postinoculation) and a delayed antibody response to feline oncornavirus-associated cell membrane antigen. The distribution of FeLV group specific antigen in tissues of MPA-treated, FeLV-inoculated cats suggested that corticosteroids enhanced susceptibility to FeLV by impairing early viral containment in the reticuloendothelial and lymphoid tissues. (23 refs)

79-5760 Genetic Relatedness of Mammalian Type C Helper and Replication-defective Transforming Viruses.

(Eng) Stephenson, J. R. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Khan, A. S.; Deobagkar, D. N.; Reynolds, F. H.; Reynolds, R. K.; Sacks, T. L. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, E. W., ed. (New York; Elsevier): 590 pp.; 95-113; 1978.

Cells nonproductively transformed by diverse replication-defective transforming viruses were analyzed for the expression of C-type helper virus proteins. Cell lines nonproductively infected by various mammalian transforming virus isolates express different numbers of C-type viral *gag* gene-coded proteins in a progressive fashion from the 5' to the 3' end of the *gag* gene. In cells transformed by feline sarcoma virus (FeSV) or by Abelson murine leukemia virus (A-MuLV), the two amino terminal *gag* gene-coded proteins, p15 and p12, are initially expressed in the form of polyproteins of around 110,000-130,000 mol wt. A similar, although somewhat smaller (100,000-110,000 mol wt), p15-p12-containing polyprotein has also been found in mink cells transformed by the recently described T8 isolate of the mink cell focus-forming MuLV. The viral-coded nature of the A-MuLV polyprotein is established by in vitro translation. These high-mol wt precursors are highly acidic; they undergo posttranslational cleavage, giving rise to a 25,000-mol wt intermediate cleavage product containing p15 and p12, and they lack detectable immunologic cross-reactivity with p30, p10, gp70 or reverse transcriptase. In the feline system, a 60,000-mol wt cleavage product of the initial 110,000- to 130,000-mol wt precursor has been shown to possess immunologic cross-reactivity with the tumor-specific feline oncornavirus-associated cell membrane antigen, which suggests that this viral-coded protein contains transformation-specific sequences. (39 refs)

79-5761 Incorporation of HLA Antigens into the Envelope of RNA Tumor Viruses Grown in Human Cells. (Eng)

Azocar, J. (Dept. Microbiology, Harvard Univ. Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); Essex, M. *Cancer Res* 39(9): 3388-3391; 1979.

Human lymphoblastoid cell lines productively infected with feline leukemia virus (FeLV) were studied to determine whether human

cell antigens are incorporated into virions. Fetal bovine sera plus rabbit complement or undiluted preinoculation rabbit sera plus complement were not cytotoxic for the infected or uninfected RPMI-8042 or HSB-2 cell lines. Rabbit sera collected 1 wk after final immunization with RPMI-8042 were cytotoxic for RPMI-8042 cells, and sera collected 1 wk after final immunization with HSB-2 cells were cytotoxic for HSB-2 cells. All of the FeLV-infected cells were positive for membrane fluorescence with goat anti-FeLV:fluorescein isothiocyanate (FITC). Antigenic cocapping was observed in the same location when the cells were treated with the approximate anti-HLA sera and anti-human IgG: rhodamine. Absorption of rabbit antisera produced against HSB-2 cells with uninfected HSB-2 cells greatly reduced the neutralizing activity of the antiserum as directed to FeLV grown in the same cells. The same effect was observed with the RPMI-8042 line. When antiserum against FeLV-infected HSB-2 cells was absorbed with uninfected HSB-2 cells, this antiserum retained neutralizing activity for FeLV. Antisera to the A determinant A1 had a greater effect in neutralizing virus produced by HSB-2 than did the antisera to the B determinant B12. When virus derived from the RPMI-8042 line was tested with antisera to HLA-A29 or HLA-A1 (which are present in these cells) plus rabbit complement, a 40%-59% reduction in infectivity was obtained compared with a control treatment using either antiserum to an unrelated antigen, normal serum, or complement alone. (13 refs)

79-5762 In Vitro Transformation by Bovine Papilloma Virus. (Eng) Meischke, H. R. (Bureau Animal Health, Dept. Primary Industry, Canberra, Australia). *J Gen Virol* 43(3): 473-487; 1979.

Bovine papilloma virus (BPV) was investigated with regard to such parameters of cell transformation as the range and sources of transformation permissive cells, the precision and sensitivity of transformation assays, the inhibition of in vitro transformation, and the time-temperature inactivation of BPV. BPV from fibropapilloma consistently transformed cell cultures from fetal bovine palate, conjunctiva, and vascular meninges, as well as skin cultures from near-term fetuses. When cells were infected in suspension, complete adsorption of BPV took 3-4 days, while when the cells were infected as a monolayer, adsorption took up to 7 days. The transformed cultures demonstrated a consistent increase in longevity when compared with controls (2.5- to 3-fold increase in lifespan). No colonies were formed by transformed cells during a 4-wk observation period after suspension in 0.3% agar. There was a considerable variation in the optimal time determined for reading assay plates between the cell cultures. When cells were infected in suspension, wisps first appeared 7-10 days later; when they were infected as monolayers, wisps first appeared after 11-14 days. Transformation was induced in the four most studied cultures (two skin and one each meninges and conjunctiva) by BPV extracted from cutaneous, teat, and alimentary fibropapilloma of cattle. No significant differences were observed between titers of pasteurized and untreated virus isolates. A 10-fold reduction in transformation titer occurred after 4 hr when one fibropapilloma-derived virus isolate was held at 60 C for various lengths of time. All detectable activity was lost when the same isolate was held at 80 C for 30 min. BPV-like viruses were found in milk samples from six separate dairies. It is shown that transformation inhibition activity may be adsorbed from high titer sera using BPV-induced tumor cells or in vitro transformed cells, but not with various virus suspensions. (22 refs)

79-5763 Amino-terminal Sequence of Bovine Leukemia Virus Major Internal Protein: Homology with Mammalian

Type C Virus p30 Structural Proteins. (Eng) Oroszlan, S. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Copeland, T. D.; Henderson, L. E.; Stephenson, J. R.; Gilden, R. V. *Proc Natl Acad Sci USA* 76(6): 2996-3000; 1979.

The amino acid composition, the COOH-terminal amino acid, and the NH₂-terminal amino acid sequence of the first 55 residues of the major internal structural protein, p24, of bovine leukemia virus (BLV) were determined to define the similarity of BLV to other mammalian retroviruses. The compositional data and the results of end-group analysis revealed that, although BLV p24 is chemically distinct, it more closely resembles the p30 structural proteins than the other *gag* gene products of mammalian retroviruses. BLV p24 shares the common NH₂-terminal proline and COOH-terminal leucine but lacks the common prolylleucylarginine tripeptide and the larger conserved region found near the NH₂ terminus of all mammalian C-type viral p30's. Alignment of the amino acid sequence of BLV p24 with the previously determined sequence of feline leukemia virus p27 revealed a statistically significant sequence homology. A more distant relationship was found between BLV p24 and other mammalian p30's. The finding of a definite sequence homology between BLV p24 and mammalian C-type virus p30's clearly establishes the origin of these contemporary viral proteins from common progenitor genes. (42 refs)

79-5764 Elevated Titer of Antibodies to Simian Sarcoma Virus Envelope Antigen (gp70) and Normal Response to Influenza Virus in Untreated Danish Hodgkin's Patients. (Eng) Ebbesen, P. (Dept. Tumor Virus Res., Univ. Copenhagen, Copenhagen, Denmark); Due, C.; Hesse, J.; Kurth, R.; Noble, G. R.; Gallagher, R.; Voller, A.; Jensen, G. *Int J Cancer* 24(1): 1-5; 1979.

Tests for serum antibodies to Epstein-Barr virus (EBV), six strains of influenza virus, and simian sarcoma virus/simian sarcoma-associated virus [SSV(SSAV)] antigens were performed in 130 untreated Danish Hodgkin's disease (HD) patients and paired with age- and sex-matched controls. HD sera showed significantly elevated titers against EBV and an increased incidence and increased mean titer of antibodies to the envelope glycoprotein (gp 70) of SSV(SSAV), whereas testing against the influenza viruses revealed no differences between HD patients and controls. A focus-reduction assay demonstrated a low incidence in HD patients and controls of sera with neutralizing effects against SSV(SSAV) and the baboon C-type virus component of the human HL-23 virus complex, which seemed to be coupled to the HL-A antigen W19. (44 refs)

79-5765 Viral Etiology of Osteomyelofibrosis, a Preleukemic Syndrome of Childhood. (Ger) Chandra, P. (Abteilung für Molekularbiologie, Zentrum der Biologischen Chemie, Theodor-Stern-Kai 7, 6 Frankfurt (Main) 70, W. Germany); Steel, L. K.; Laube, H.; Kornhuber, B. *Klin Paediatr* 191(2): 156-174; 1979.

Three cellular DNA polymerases and a reverse transcriptase (RT) were isolated from the surgically removed spleen of a patient with osteomyelofibrosis. This is the first report of the identification and characterization of a tumor-specific enzyme from the tissue of a patient with a preleukemic syndrome. The mol wt of the RT was 70,000, and the mol wts of the polymerases were 40,000, 150,000,

and 100,000. The RT was identified by its RNase sensitivity and its ability to transcribe the heteropolymer region of 70S RNA from Rauscher murine leukemia virus (R-MuLV). The conclusion that RT was isolated was strengthened by the observations that poly C.oligo dG stimulated the enzyme activity, and the RT's from simian sarcoma and Gibbon ape leukemia viruses showed several similarities to the new RT in serological tests. The RT's from R-MuLV and avian myeloblastosis virus produced a weak cross-reaction with the new RT in immunological tests, but the RT from the membrane of human acute lymphatic leukemia cells produced a strong reaction. The three DNA polymerases that were isolated did not produce these reactions. The strong cross-reaction with the RT from human leukemia cells indicates that antibodies to this enzyme could be produced and used to detect leukemia cells in patients before the appearance of clinical signs of leukemia. (49 refs)

79-5766 Characterization of Infection and Replication of Mason-Pfizer Monkey Virus in Human Cell Cultures. (Eng) Fine, D. L. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Clarke, G. C.; Arthur, L. O. *J Gen Virol* 44(2): 457-469; 1979.

The infection and replication of the Mason-Pfizer monkey virus (MPMV) in cells of the human rhabdomyosarcoma cell line, A204, were studied. A204 cultures inoculated with 10⁻⁴ to 10⁻⁶ virus dilutions did not express reverse transcriptase (RT) until after subculturing, but productive infection could be accomplished at virus particle (VP) input multiplicities as low as approx 6 x 10⁻² VP/cell. MPMV expression was stable with continuous culture passage and after freeze-thawing, but virus infectivity was destroyed by UV irradiation and by sonication. MPMV replication and production in A204 cultures was cell-cycle-dependent, the highest levels of RT activity coinciding with the peak of mitosis and early G₁. The release of MPMV from infected cells appeared to be dependent upon the passage of cells through mitosis. Inhibition of MPMV production in cells arrested in mitosis appeared to be due to a limiting step prior to virus maturation. The information gained in this study was applied in the isolation of MPMV-like viruses from naturally and experimentally infected Rhesus monkeys following co-cultivation of tissues with A204 cell cultures. (52 refs)

79-5767 Physicochemical Properties and Restriction Maps of Simian Adenovirus Type 38 DNA. (Eng) Dimitrov, D. H. (Lab. Biochemistry, D. I. Ivanovsky Inst. Virology, Moscow D-98, USSR); Dubitchov, A. G.; Naroditsky, B. S.; Dreizin, R. S.; Tikchonenko, T. I. *J Gen Virol* 44(1): 69-80; 1979.

The physicochemical properties and restriction endonuclease maps of simian adenovirus type 38 (Ad38) DNA were studied. The sedimentation constant of Ad38 DNA was estimated to be 31.6S. The intrinsic viscosity averaged 86.5 deciliters/g, and the length of the molecule was 10.6 μm. The av mol wt was 21.5 x 10⁶, which agreed well with the value derived from the length of the molecule (21.4 x 10⁶) and with the value of 21.2 x 10⁶ determined by the relative electrophoretic mobility of the DNA fragments produced by restriction endonucleases *EcoRI*, *SalI*, and *BglII*. The buoyant density of the DNA in cesium chloride and cesium sulfate was 1.7185 and 1.4295 g/ml, respectively. The melting temperature of the DNA was 93.5 °C, and the guanine-cytosine content was 59.3%. *BglII* cleaved the Ad38 DNA at three sites, producing four fragments with mol wts of 9.3 (A), 5.6 (B), 3.3 (C), and 2.9 (D) x 10⁶, respectively. After treatment with *EcoRI* and *SalI*, the DNA was cleaved into five and six fragments, respectively. The mol wts

of the *Eco*RI fragments were 8.2 (A), 6.5 (B), 4.0 (C), 1.27 (D), and 1.07 (E) $\times 10^6$, respectively, and those for the *Sa*II fragments were 6.5, 5.4, 4.2, 2.8, 2.5, and 0.25 $\times 10^6$, respectively. The sequence of fragments within the Ad38 DNA molecules was BDCA for *Bgl*II, and BCEAD for *Eco*RI. (18 refs)

79-5768 *Herpesvirus papio*: State and Properties of Intracellular Viral DNA in Baboon Lymphoblastoid Cell Lines. (Eng) Falk, L. (Dept. Tumor Biology, Karolinska Inst., S-104-01 Stockholm, Sweden); Lindahl, T.; Bjursell, G.; Klein, G. *Int J Cancer* 24(1): 75-79; 1979.

The physical state of the viral DNA in lymphoblastoid cell lines derived from baboon species that harbor *Herpesvirus papio* (HVP), an indigenous B-lymphotropic virus of baboons, was investigated. HVP shares cross-reacting viral capsid and early antigens with Epstein-Barr virus (EBV), and HVP DNA and EBV DNA show partial sequence homology. EBV-specific complementary RNA was used as a probe to investigate the physical state of the HVP DNA component in baboon lymphoblastoid cells after fractionation of cellular DNA by density gradient centrifugation. Five virus-producing cultures contained both free and integrated HVP DNA sequences, but one nonproducing cell line had two or three viral genome equivalents per cell in apparently integrated form. Further analysis of one virus-producing line showed that the free HVP DNA fraction was composed of both linear and circular viral DNA. Contour length measurements of HVP circular DNA molecules by electron microscopy revealed that they were similar in length to the EBV circular DNA present in human lymphoblastoid cells. (17 refs)

79-5769 Familial Herpes Simplex Infection Associated with Activation of the Complement System. (Eng) Kapadia, A. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Gupta, S.; Good, R. A.; Day, N. K. *Am J Med* 67(1): 122-126; 1979.

The peripheral blood lymphocytes from a female patient with severe recurrent herpes infection responded by proliferation to herpes simplex antigen but failed to produce leukocyte migration inhibition factor. Herpes simplex antibody titers increased during active infection. Total hemolytic complement, the third, fifth, sixth, and seventh components of complement, and factor B were dramatically reduced; the first, second, and fourth complement components were within normal limits. In members of her family that had a history of recurrent herpes simplex, one or more of complement components 5, 6, or 7 was reduced. (24 refs)

79-5770 Separation and Characterization of Herpes Simplex Virus Type 1 Immediate-Early mRNA's. (Eng) Watson, R. J. (Lab. Molecular Virology, NCI, Bethesda, MD 20205); Preston, C. M.; Clements, J. B. *J Virol* 31(1): 42-52; 1979.

Polyadenylated immediate-early transcripts of herpes simplex virus type 1, made in BHK cells infected and maintained in the presence of cycloheximide, were separated on denaturing agarose gels containing methyl mercuric hydroxide. Three virus-specific messenger (mRNA) RNA bands of estimated sizes 4.7, 3.0, and 2.0 kilobases (kb) were detected, and these mRNA's were mapped on the virus genome and also used to direct protein synthesis *in vitro*. The 4.7- and 3.0-kb mRNA's hybridized predominantly to certain

DNA fragments which are located in the short and long repetitive regions of the genome, respectively, whereas the 2.0-kb mRNA mapped to three discrete regions of the virus DNA. *In vitro* translation of these separated mRNA size classes indicated that the 3.0-kb mRNA specified the synthesis of virus polypeptide Vmw 110, whereas the 2.0-kb mRNA's specified Vmw 68, 63, and 12. The synthesis of small amounts of Vmw 175 was specified by the 4.7-kb mRNA. In contrast with the mRNA's which specify these other immediate-early polypeptides, that specifying Vmw 12 is much larger than required for its coding sequences. (25 refs)

79-5771 Properties of Herpes Simplex Virus DNA Polymerase and Characterization of Its Associated Exonuclease Activity. (Eng) Knopf, K. W. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany). *Eur J Biochem* 98(1): 231-244; 1979.

The large-scale purification of herpes simplex virus type 1 (HSV-1) DNA polymerase is described, along with the characterization of the exonuclease activity associated with this enzyme. HSV-1 DNA polymerase was isolated from infected African green monkey kidney cells. After DNA-cellulose chromatography, the enzyme showed a specific activity of 48,000 units/mg protein. Three major single polypeptides with mol wts of 144,000, 74,000, and 29,000 were copurified with the enzyme activity at the DNA-cellulose step. By its chromatographic behavior and by template studies, the HSV DNA polymerase activity was clearly distinguishable from cellular α , β , and γ DNA polymerase activities. Two exonucleolytic activities were found in the DNA-cellulose enzyme preparation. The main exonucleolytic activity, which degraded both single- and double-stranded DNA to deoxynucleoside 5'-monophosphates, was separated by subsequent velocity sedimentation. The remaining exonucleolytic activity was not separable from the HSV DNA polymerase by several chromatographic steps and by velocity sedimentation at high ionic strength. This novel exonuclease and HSV DNA polymerase were equally sensitive to phosphonoacetic acid and Zn^{2+} ions, inhibitors of the viral polymerase. Similar to the 3'- to 5'-exonuclease of prokaryotic DNA polymerases and mammalian DNA polymerase δ , the HSV polymerase-associated exonuclease catalyzed the removal of 3'-terminal nucleotides from the primer/template as well as the template-dependent conversion of deoxynucleoside triphosphates to monophosphates. (33 refs)

79-5772 Modulation of Herpes Simplex Virus Replication in Adenovirus Transformed Cells. (Eng) Stenberg, R. (Dept. Microbiology, Univ. Colorado Medical Center, Denver, CO 80262); Spector, D.; Pizer, L. *J Gen Virol* 44(2): 297-309; 1979.

The ability of herpes simplex virus type 1 (HSV-1), strain HF, to replicate in adenovirus type 5 (Ad 5)-transformed cells was examined, in order to determine whether the presence of an integrated adenovirus genome or the cell type plays the major role in restricting the ability of HSV to replicate. Ad-transformed human and hamster cells maintained their permissiveness for HSV replication, while rat cells were either nonpermissive or showed a strong temperature dependence for the production of infectious HSV. One line of Ad 5-transformed rat cells, 107, allowed HSV to replicate at 34 C but not at 37 C and was examined in detail. At 37 C, virus-specific DNA synthesis was greatly reduced, but all of the late virus structural proteins could be observed after sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Shut-off of host macromolecular synthesis was less efficient after HSV infec-

tion of 107 cells than after infection of more permissive cells, such as the nontransformed rat embryo fibroblast (REF) line. The data show that interactions between HSV and the host cell are perturbed when the cell is transformed by Ad 5 and that this disruption reduces the yield of virus progeny. Whether endogenous viruses influence the fate of HSV infection and the establishment and maintenance of latency should be examined. (23 refs)

79-5773 Presence of Herpes Simplex Virus Type 2 DNA in Hamster Cells Oncogenically Transformed by Ultraviolet-inactivated Virus. (Eng) Bibor-Hardy, V. (Institut du Cancer de Montreal, Centre Hospitalier Notre-Dame, 1560 est, rue Sherbrooke, Montreal, Quebec H2L 4M1, Canada); Kessous, A.; Simard, R. *Can J Biochem* 57(6): 867-872; 1979.

Herpes simplex virus type 2 (HSV-2) DNA was detected by molecular hybridization techniques in Syrian hamster embryo fibroblast cells transformed by UV-irradiated virus. At early passages after the cells were cloned in soft agar, about 40% of the HSV-2 genome was present in all the transformed cell lines at one to six copies per cell. In cell lines derived from tumors induced by these cells, the same percentage of the HSV-2 genome was found with a more uniform number of copies (between 2 and 3). Thus, the presence of viral DNA seems to be necessary for maintenance of the transformed state in these cell lines. (31 refs)

79-5774 Production of Tubular Structures in Vero Cells Infected with Herpes Simplex Virus Type 2: Effects of Ultraviolet Light Irradiation and Antimetabolites. (Eng) Iwasaka, T. (Dept. Microbiology, Sch. Medicine, Kyushu Univ., Fukuoka 812, Japan); Oda, H.; Mori, R.; Miyazono, J.; Nagafuchi, S. *J Gen Virol* 44(1): 57-67; 1979.

The nature of the tubular or filamentous structures specifically found in herpes simplex virus type-2 (HSV-2)-infected cells was investigated by determining the multiplication of HSV-2 in Vero cells cultured in the presence of varying concentrations of cytosine arabinoside (Ara-C) and cycloheximide (CH), inhibitors of DNA synthesis and protein synthesis, respectively. At 60 µg/ml, Ara-C inhibited the multiplication of HSV-2 by >99% and also prevented the appearance of tubular structures and virus particles in the nuclei of infected cells. Nevertheless, the synthesis of virus-specific surface antigens of HSV-2-infected Vero cells was not reduced, as revealed by the fluorescent antibody technique. On the other hand, 10 µg/ml CH inhibited the appearance of tubular structures and virus particles and the synthesis of virus-specific surface antigens by >99%. These observations strongly suggest that the appearance of tubular structures is one of the late events in virus multiplication. To measure the comparative genome size needed to produce membrane antigens, tubular structures, and infectious centers, the effect of UV inactivation of HSV-2 on these processes was studied. After UV irradiation, the capacity to induce tubular structures was inactivated at a slower rate than the capacity to form infectious centers, but at a faster rate than the capacity to induce surface antigens. Furthermore, more tubular structures could be induced by UV-inactivated virus than by nonirradiated virus, which was diluted to the same infectivity as the UV-irradiated virus. These results indicate that expression of the entire genome is not required for the production of tubular structures. (20 refs)

79-5775 Analysis of Chromosomes, Nucleic Acids, and Polypeptides in Hamster Cells Transformed by Herpes Simplex Virus Type 2. (Eng) Kessous, A. (Institut du

Cancer de Montreal, Centre Hospitalier Notre-Dame, 1560 est, rue Sherbrooke, Montreal, Quebec H2L 4M1, Canada); Bibor-Hardy, V.; Suh, M.; Simard, R. *Cancer Res* 39(8): 3225-3234; 1979.

Syrian hamster embryo fibroblasts were oncogenically transformed by UV-inactivated herpes simplex virus type 2, and data obtained from comparative studies of 2/18 clones isolated and their tumor derivatives are reported. Karyotype analysis revealed different chromosome patterns in the two clones and a tendency toward hypodiploidy in the tumor derivatives. All of these cell lines were shown by molecular hybridization to contain 40% of the HSV genome in several copies. The viral DNA sequence complexity was retained in the tumor derivatives, but a decrease in copy number was observed. Viral RNA's were detected by in situ hybridization in all lines tested. Viral antigens could be observed in these transformed cells by immunofluorescence. Finally, polypeptide analysis showed three reproducible differences between normal and transformed cells: (1) a polypeptide with a mol wt of 200,000 was detected in smaller quantities or not at all in the transformed cells; (2) a polypeptide with a mol wt of 84,000 was consistently observed in most transformed clones but not in normal cells; (3) a polypeptide with a mol wt of 42,500 was present only in transformed cells and their tumor derivatives. (46 refs)

79-5776 Studies Demonstrating the Immunological Identity of the Tumor-associated Antigen AG-4 with a Virion Envelope Protein. (Eng) Strnad, B. C. (Div. Comparative Medicine, Dept. Biochemistry and Biophysics, Johns Hopkins Univ. Sch. Medicine, Hygiene and Public Health, Baltimore, MD); Smith, M. F.; Aurelian, L. *IARC Sci Publ* 24(1): 203-213; 1978.

The immunological identity of the cervical tumor-associated antigen AG-4 is reviewed. Herpes simplex virus type 2 (HSV-2)-infected cell protein No. 10 (ICP 10) was purified by acrylamide gel electrophoresis and found to fix complement with IgM from AG-4 positive human sera. Preincubation of AG-4 antigen with Fab' from anti-ICP 10 completely blocked its ability to fix complement with AG-4 positive sera, thus demonstrating the immunological identity of ICP 10 and AG-4. IgG from anti-ICP-10 sera fixed complement with HSV-2, and their complement fixing potential for AG-4 was absorbed with virions. Autoradiography demonstrated that ICP 10 is an envelope protein, and AG-4 was shown to occupy a site on the envelope surface which is sterically removed from those involved in neutralization and infectivity. (11 refs)

79-5777 Characterization of a Tree Shrew Herpesvirus Isolated from a Lymphosarcoma. (Eng) Darai, G. (Institut für Medizinische Virologie, Universität Heidelberg, Im Neuenheimer Feld 324, 69 Heidelberg, W. Germany); Matz, B.; Schroder, C. H.; Flugel, R. M.; Berger, U.; Munk, K.; Gelderblom, H. *J Gen Virol* 43(3): 541-551; 1979.

Data are given on the isolation and characterization of a herpesvirus isolated from a lymphosarcoma culture of tree shrews (*Tupaia belangeri*) and termed *Tupaia* herpesvirus 2 (THV-2). Electron microscopy of THV-2 revealed the presence of virus particles with nucleocapsids of about 100 nanometers surrounded by large envelopes compatible with virions of the herpesvirus group. An extensive host range study revealed that *Tupaia* embryonic fibroblasts are the cells of choice for the efficient propagation of THV-2. This cell line was used for the continued propagation and

plaque assay of THV-2. The mol wt of the virus DNA was found to be 100×10^6 . The buoyant density of THV-2 was 1.724 g/ml. The DNA of THV-2 was compared with the DNA of herpes simplex virus (HSV) and with that of a herpesvirus isolated previously from apparently healthy tree shrews (THV-1) using the restriction endonuclease *EcoRI*. The cleavage pattern of THV-2 DNA resulted in DNA fragments that were different from those of HSV-1 DNA and from those of THV-1 DNA. (22 refs)

- 79-5778 Etiological and Clinical Data on Hemangiomas. (Hun) Frank, K. (Gyermekklinika, Orvostovábbképző Intézet, Budapest, Hungary). *Orv Hetil* 120(22): 1301-1302; 1979.

Cytomegalovirus (CMV) was found in the serum of a premature baby with hemangiomas and somatic and mental retardation. Immunoelectrophoresis revealed an elevated IgM level. The findings suggest a possible link between hemangiomas and CMV infection. In general, hemangiomas may be the angiopathic consequence of maternal infection. (17 refs)

- 79-5779 Mapping of Putative Transforming Sequences of EBV DNA. (Eng) Kieff, E. (Section Infectious Disease, Dept. Medicine, Univ. Chicago, Chicago, IL); Raab-Traub, N.; Given, D.; King, W.; Powell, A. T.; Pritchett, R.; Dambaugh, T. *IARC Sci Publ* 24(1): 527-552; 1978.

The linkage of restriction enzyme fragments of Epstein-Barr virus (EBV) DNA (B95-8 strain) has been determined. Two approaches are being employed to define which EBV DNA sequences are needed to initiate and maintain the transformation of lymphocytes to lymphoblasts capable of long-term growth in culture. The first approach is to determine the differences between the DNA of EBV strains which possess transforming capacity and the DNA of the HR-1 strain which cannot transform. The data indicate that EBV (HR-1) DNA lacks approximately 2.3×10^6 daltons of DNA contained largely in the *HsuI* B and *EcoRI* (J-K) and A fragments of EBV (B95-8) DNA and in the *EcoRI* A and *HsuI* B fragment of the W91 strain. The DNA common to *HsuI* B and *EcoRI* A fragments lies between 27 and 42×10^6 daltons from the *HsuI* A end of the molecule. This finding is compatible with the hypothesis that the inability of the HR-1 strain to transform is due to the absence of DNA needed for transformation. The second approach is to identify and map the DNA encoding polyadenylated viral RNA in cultures of reproductively infected cells which contain the EBV nuclear antigen (EBNA) and show no evidence of abortive or productive infection. Previous data have indicated that viral RNA species encoded by 5% of the viral DNA are adenylated and identified in the polyribosomes of reproductively infected cells. The data indicate that these RNAs are encoded primarily by the *HsuI* A (and to a lesser extent, B) fragment of EBV (B95-8) DNA. This would place the DNA encoding the viral RNA processed in reproductively infected cells adjacent to and possibly overlapping the small DNA segment deleted from the DNA of the nontransforming HR-1 strain. (27 refs)

- 79-5780 Sites of Sequence Variability in Epstein-Barr Virus DNA from Different Sources. (Eng) Rymo, L. (Dept. Clinical Chemistry, Gothenburg Univ., 40033 Gothenburg, Sweden); Lindahl, T.; Adams, A. *Proc Natl Acad Sci USA* 76(6): 2794-2798; 1979.

The intracellular Epstein-Barr virus (EBV) DNA present in virus-transformed cells was partly purified from 23 cell lines or biopsies of Burkitt's lymphoma, nasopharyngeal carcinoma, infectious mononucleosis, or healthy carrier origin. This DNA was cleaved into fragments (A-K) with mol wts between 1×10^6 and 30×10^6 with the restriction enzyme *EcoRI*, and the fragments were analyzed by standard methods involving agarose gel electrophoresis, transfer to nitrocellulose filters, and hybridization with radioactive EBV DNA or complementary RNA. Sequence variability among different EBV DNA isolates was largely confined to the A, C, and I fragments. These results are discussed in relation to the linkage map of the *EcoRI* fragments of EBV DNA. The *EcoRI* cleavage pattern of intracellular viral DNA of an EBV-like virus from baboon cells, *Herpesvirus papio*, was entirely different from that of human EBV isolates. The results show that, at the present level of resolution, no obvious disease-related differences could be discerned among EBV DNA isolates of tumor or nontumor origin. However, more subtle sequence differences within the EBV genome may still be of critical biological importance. (27 refs)

- 79-5781 Relationship Between Epstein-Barr Virus Genome Number, Amount of Nuclear Antigen, and Early Antigen Inducibility in Diploid and Tetraploid Lymphoma Cells of Related Origin. (Eng) Shapiro, I. M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Luka, J.; Andersson-Anvret, M.; Klein, G. *Intervirology* 12(1): 19-25; 1979.

Among several near-diploid and near-tetraploid Raji sublines and somatic Raji/Raji hybrids, a linear relationship was found between the number of Epstein-Barr virus (EBV) genome copies and the relative amount of EBV-determined nuclear antigen per cell. Inducibility of the viral cycle by iododeoxyuridine and by P3HR-1 virus superinfection may be related to the number of resident EBV genome copies per haploid target cell. It is suggested that cells with ≤ 25 EBV genome equivalents per diploid chromosome set will have a very low inducibility. An increased number of EBV genome copies may increase the chances for initiation of the viral cycle. Alternatively, the number of EBV genome copies and inducibility may be regulated by coordinated controls. (15 refs)

- 79-5782 Mode of Integration of Epstein-Barr Virus Genome into Host DNA in Burkitt Lymphoma Cells. (Eng) Kolias, S. I. (Theagenion Medical Inst., Thessaloniki, Greece). *J Gen Virol* 44(2): 573-576; 1979.

The integrated Epstein-Barr virus (EBV) DNA found in Burkitt lymphoma (BL) cells was studied. DNA was fractionated by cesium chloride (CsCl) density gradient centrifugation and characterized by hybridization with EBV complementary RNA (cRNA). In neutral CsCl gradients, high mol wt DNA from an African BL biopsy showed a reduction in size which caused a shift of the EBV sequences to higher densities. In the case of high-mol-wt DNA from the SU-AmB-2 BL cell line, a similar reduction in size of the DNA had no apparent effect on the density of DNA. These results show that in the case of the African BL, EBV DNA sequences integrated into the host genome are very large, whereas EBV DNA integrated into SU-AmB-2 cells is very small. It is concluded that few sites of integration exist in the cells of the African BL biopsy, whereas cells of the American SU-AmB-2 line contain a larger number of integration sites. (10 refs)

- 79-5783 Growth of Diploid, Epstein-Barr Virus-carrying Human Lymphoblastoid Cell Lines Heterotrans-

planted into Nude Mice under Immunologically Privileged Conditions. (Eng) Giovanella, B. (Cancer Res. Lab., St. Joseph Hosp., Houston, TX 77002); Nilsson, K.; Zech, L.; Yim, O.; Klein, G.; Stehlin, J. S. *Int J Cancer* 24(1): 103-113; 1979.

Eighteen diploid Epstein-Barr virus-carrying human lymphoblastoid cell lines (LCL) of presumed nonneoplastic origin were inoculated intracerebrally into nude mice. All 18 lines grew, killing their hosts within 7-25 days except for 2 that grew more slowly. At autopsy, the brains of these mice were found to be invaded by infiltrating lymphomas. Sixteen of the lymphomas, when recultured in vitro, gave rise to cell lines with growth properties and a morphology indistinguishable from those of the inoculated LCL. Chromosome examinations of seven cell lines that grew as lymphomas in the brain showed that three were still normal diploid on reimplantation, whereas the remaining four had become aneuploid. When four lines derived from the intracerebral lymphomas (2 diploid, 1 aneuploid, and 1 untested) were injected sc into adult nude mice, sc into newborn nude mice, or intracerebrally into adult normal mice, none of them grew. However, they grew rapidly when they were injected sc into newborn nude mice. One of these lines, U-1450, was injected sc into adult nude mice treated with antilymphocyte serum. Small nodules developed at the inoculation site. A cell line (1450 ALSAD) was cultured from one nodule. It was morphologically indistinguishable from the line of origin. The lines obtained from nude mice inoculated with polyclonal LCL seemed to have a restricted clonal representation, but they were not monoclonal, as evidenced by analyses of their immunoglobulin synthesis pattern. (40 refs)

- 79-5784 In Vitro Transforming Activity of Epstein-Barr Virus (EBV). II. Differences Between M81 and B95-8 EBV Strains. (Eng) Desgranges, C. (150 Cours Albert Thomas, 69372 Lyon, France); Lavoue, M. F.; Patet, J.; de-The, G. *Biomedicine* 30(2): 102-108; 1979.

Lymphocytes from 38 human cord blood and 9 adult circulating blood samples were infected in parallel either with the B95-8 Epstein-Barr virus (EBV) strain (produced by cotton-top marmoset lymphocytes transformed by EBV originating from an infectious mononucleosis line) or with the M81 EBV strain (produced by *Callithrix jacchus* marmoset lymphocytes transformed by EBV originating from a nasopharyngeal carcinoma derived line). Significant differences observed in the lymphoblastoid lines obtained involved cell morphology, cell growth and synthesis of viral antigen. Cord blood lymphocytes infected with M81 virus resulted in lymphoblastoid lines where early antigen and viral capsid antigen synthesis and production of virions took place, whereas this was not observed in B95-8-induced lines. (16 refs)

- 79-5785 Antigenic Relationships Between Polypeptides Derived from Plantar and Hand Wart Viruses. (Eng) Staquet, M. J. (F.R.A. INSERM No. 11, Recherche Dermatologique et Immunologie, Clinique Dermatologique, Hopital Ed. Herriot, 69374 Lyon Cedex 2, France); Viac, J.; Thivolet, J. *J Gen Virol* 43(3): 713-717; 1979.

A comparative study was made of the antigenicity and immunogenicity of various polypeptides derived from plantar and hand wart viruses. Guinea pigs immunized with polypeptides derived from plantar and hand wart viruses (PV and HV) developed both humoral and cell-mediated immunity. The specificity of the antiserum was determined by indirect im-

muno fluorescence (IF) tests, and cellular immunity was determined by id tests. Although whole PV and HV particles appeared to be immunologically analogous, they had different polypeptide patterns, as shown by analysis on acrylamide slab gels. In particular, the P2 polypeptide (major virus protein) of PV had a different mol wt (56,750) than that of HV (54,500), and it induced high antibody titers in the animals. In addition, the immune sera specifically labeled wart substrates, as shown in the IF test, demonstrating that no cross humoral reaction occurs between these two polypeptides. Furthermore, a delayed hypersensitivity reaction was observed in P2 polypeptide-inoculated guinea pigs when whole particles were introduced in skin tests, but a cross-reactivity between PV and HV was noticed at the cellular level. Virus particles isolated from the lesions of a patient bearing extensive common hand warts possessed all the biochemical and immunological characteristics of PV, particularly with regard to the P2 polypeptide. Such a case may represent plantarlike warts located on the hands. (18 refs)

- 79-5786 Sequence from Early Region of Polyoma Virus DNA Containing Viral Replication Origin and Encoding Small, Middle and (Part of) Large T Antigens. (Eng) Soeda, E. (Nat'l. Inst. Genetics, Misima 411, Japan); Arrand, J. R.; Smolar, N.; Griffin, B. E. *Cell* 17(2): 357-370; 1979.

The sequence of about one-third of the polyoma virus (PV) genome is presented. This sequence covers the origin of replication of two large plaque strains (A2 and A3) of PV. The two strains differ by 11 base pairs in the origin region. A model for replication is suggested. The sequence probably also covers the entire coding region of two PV early proteins, small and middle tumor (T) antigens, as well as part of the coding region for large T antigen. Over a small region of the DNA, all three coding frames contain termination codons, which suggests a need for spliced early messenger RNA's. In another region of the DNA, two coding frames can be used. Correlation with protein data suggests that one frame codes for part of middle T antigen and the other for part of large T antigen. (47 refs)

- 79-5787 Role of Interferon in the Pathogenesis of Virus Diseases in Mice as Demonstrated by the use of Anti-Interferon Serum. VI. Polyoma Virus Infection. (Eng) Gresser, I. (Institut de Recherches Scientifiques sur le Cancer, Villejuif, France); Maury, C.; Kress, C.; Blangy, D.; Maunoury, M. T. *Int J Cancer* 24(2): 178-183; 1979.

The effect of a single ip injection of potent sheep anti-mouse interferon globulin (SAIG, 50-100 μ l) on polyoma-virus (PV)-induced early runting disease and tumor formation was studied using Swiss mice. Mice treated with PV (50 μ l ip immediately before SAIG during the first 24 hr of life) grew as well as mice treated with PV + SAIG for the first 11 days, after which 10%-20% of the PV-treated mice and most of the PV + SAIG-treated mice were runted. Mortality during the first 2 mo was 0%-25% for the PV-treated mice and 70%-100% for the PV + SAIG-treated mice. Deaths usually occurred during the third or fourth week. Histologic examination showed no differences between mice treated with PV and those treated with PV + SAIG. The median tumor-inducing doses for the PV- and PV + SAIG-treated mice were 10^6 and 10^2 - 10^3 plaque-forming units, respectively. The tumor incidence was greater and the tumor latent period reduced in mice treated with PV + SAIG compared with those given PV alone. The sites of tumor development were similar in the two groups. The titers of virus in the thymuses and spleens of the PV

+ SAIG-treated mice were greater than those in the PV-treated mice. No interferon was demonstrated in the PV-treated mice, whether or not they were given SAIG. The results suggest that interferon is an important factor in determining the susceptibility of newborn mice to PV. (33 refs)

- 79-5788 The Colinear Alignment of the Genomes of Papovaviruses JC, BK, and SV40. (Eng) Law, M. F. (Lab. Pathology, NCI, Bethesda, MD 20205); Martin, J. D.; Takemoto, K. K.; Howley, P. M. *Virology* 96(2): 576-587; 1979.

The polynucleotide sequence homology among the DNA's of polyomaviruses JC, BK, and simian virus 40 (SV40) were analyzed under a range of nonstringent hybridization conditions. When the hybridizations were performed at $T_m - 36^\circ\text{C}$, conditions that would detect regions of homology with as much as 26% base mismatch, extensive homology was detected in all gene regions between the JC genome and both the BK and SV40 DNA's. The regions of strongest sequence homology between the genomes formed stable duplexes at $T_m - 21^\circ\text{C}$, indicating at least an 85% base match. By two-dimensional cross-hybridization of restriction endonuclease cleavage fragments of JC to both those of BK and SV40 under nonstringent conditions, it was possible to map the homologous DNA fragments of each pair of viruses with respect to each other. The physical maps of these polyomaviruses could be colinearly aligned using the conserved single *EcoRI* site in each genome as the 0 map position. The region of strongest homology among these three genomes was localized in a narrow segment (0.76 to 0.85 map unit) in the late region, which in the SV40 genome contains the codons for the N-terminal half of the minor viral protein VP2. (52 refs)

- 79-5789 The Spliced Structure of BK Virus mRNAs in Lytically Infected and Transformed Cells. (Eng) Manaker, R. A. (Lab. Molecular Virology, NCI, NIH, Bethesda, MD 20014); Khoury, G.; Lai, C. J. *Virology* 97(1): 112-121; 1979.

The messenger RNA (mRNA) molecules of human papovavirus BK virus (BKV) in lytically infected cells and in a transformed human cell culture cloned from a population infected with UV-inactivated BKV were mapped by the nuclease S1 technique. Two BKV mRNA species were synthesized in cells early after lytic infection and in virus-transformed cells. The 5' end of one RNA species (and of the other by inference) mapped at approx 0.66 map unit near the origin for DNA replication, and the 3' ends of both molecules mapped at 0.16 unit. The intervening sequences deleted from these mRNA's were located between 0.585 and 0.53 map unit for one species and between 0.535 and 0.53 map unit for the other. The map positions of these RNA's were similar to the locations of the SV40 mRNA's that encode the large tumor (T) antigen and small t antigens, respectively. The genomic locations of the late BKV mRNA species were also determined. The body sequences of the late 16S RNA mapped between 0.765 and 0.16 unit, and those of the late 19S RNA mapped between 0.765 and 0.16 unit. A significant proportion of these late transcripts contained a leader RNA transcribed from 0.70 to 0.76 map unit. The spliced late lytic BKV RNA's synthesized in both human embryonic kidney cells and African green monkey kidney cells appeared to be identical. (38 refs)

- 79-5790 Tumorigenicity and Karyotype of Rat Embryo Cell Lines Transformed by BK Virus. (Eng) Karjalainen,

H. E. (Dept. Clinical Microbiology, Univ. Kuopio, POB 138, 70101 Kuopio 10, Finland); Salmi, A.; Mantylarvi, R. A. *Acta Pathol Microbiol Scand [A]* 87(4): 245-253; 1979.

The karyotype and tumorigenicity of several rat embryo cell lines transformed by BK virus were compared. A rat embryo cell line transformed by BK virus was used to induce tumors in rats, and cell lines were established from these tumors. Other sublines were obtained by in vitro cloning of the parental line. The in vitro-cloned sublines had a low tumorigenicity. The tumorigenicity of the in vivo-selected tumor cell lines varied from high to undetectable. The tumor cell line with the highest tumorigenicity also had the highest saturation density in vitro, but otherwise there was little correlation between tumorigenicity and the in vitro characteristics of the cells. Karyotype analysis was done for two cell lines with high and low tumorigenicity, respectively, and with a near-diploid complement of chromosomes. The findings agreed with the expression-suppression model of Rabinowitz and Sachs, according to which the tumorigenicity of a cell line would depend on the balance between expression and suppression chromosomes. The suppression chromosomes seemed to be confined to Group A, the expression chromosomes to Group B. (39 refs)

- 79-5791 Polyoncogenicity and Insulinoma-inducing Ability of BK Virus, a Human Papovavirus, in Syrian Golden Hamsters. (Eng) Uchida, S. (Dept. Viral Infection, Inst. Medical Science, Univ. Tokyo, Tokyo 108, Japan); Watanabe, S.; Aizawa, T.; Furuno, A.; Muto, T. *J Natl Cancer Inst* 63(1): 119-126; 1979.

The oncogenic potential of the human papovavirus BK virus (BKV) was studied in Syrian golden hamsters. Newborn hamsters were inoculated intracerebrally with a series of purified and concentrated BKV samples from a single stock of Gardner's original strain. Most (60%-100%) of the hamsters developed various tumors 3-9 mo later. The most common of tumors were ventricular tumors (choroid plexus papillomas and ependymomas, 7%-53%), malignant insulinomas (0%-92%), and osteosarcomas (0%-50%). Fifty-nine of the 60 tumors tested were positive for tumor antigen, but virus was rescued by the cell fusion method from only 1/11 cell lines derived from these tumors. The incidence of insulinomas varied greatly with the virus sample; the two samples that showed the highest incidences (47% and 92%) originated from one parental virus stock, and samples with lower incidences (0%-9%) originated from another parental stock. These results suggest the presence of a BKV mutant(s) differing in capacity to induce insulinomas. A functional insulinoma cell line was established by injecting a minced BKV-induced insulinoma into weanling hamsters. (31 refs)

- 79-5792 Altered Nuclear Structure during Productive and Abortive Infections with SV40 DNA. (Eng) Robb, J. A. (Dept. Pathology, Green Hosp. Scripps Clinic, La Jolla, CA 92037); Rowley, R. D. *Intervirology* 12(1): 57-64; 1979.

Alterations in the nuclear morphology of five mammalian cell types following infection with simian virus 40 (SV40) DNA was studied using SV40 large-T antigen-specific immunofluorescence. A striking alteration in nuclear morphology occurred in cells infected by form I SV40 DNA (virion DNA with the virion proteins removed) but not in those infected by SV40 virions. Infection by SV40 virions was far more efficient than that by form I DNA, however. It was unlikely that SV40 or cellular DNA synthesis had any role in the genesis of the observed nuclear abnormalities; cells

with preexisting abnormal morphologies were not being selectively infected by the SV40 DNA. The finding that the formation of binucleate and fragmented nuclei following SV40 DNA infection was dependent on the cell type infected suggests that a cellular function(s) was involved in the nuclear alteration. (18 refs)

- 79-5793 Segments of Simian Virus 40 DNA Spanning Most of the Leader Sequence of the Major Late Viral Messenger RNA Are Dispensable. (Eng) Subramanian, K. N. (Dept. Microbiology, Univ. Illinois at Medical Center, Chicago, IL 60612). *Proc Natl Acad Sci USA* 76(6): 2556-2560; 1979.

The construction, by a restriction-ligation procedure, isolation, and DNA sequence of viable deletion mutants of simian virus 40 (SV40) spanning the leader sequence of the 16S messenger RNA (mRNA) are described. With the construction procedure used, the size and location of the deletions could be predetermined in vitro. The DNA products were subjected to agarose gel electrophoresis before and after ligation, to ensure that the background due to wild-type plaques is <10% of the total numbers. The deletions ranged from 20 to 223 nucleotides. All these deletion mutants were viable and grew without helper virus. The largest deletion removed the entire leader sequence except for six nucleotides at the 3' end that are probably involved in covalent linkage with the 5' end of the body of the mRNA located 937 nucleotides away. Three of the deletion mutants removed the 5' end of the leader that normally contains the cap structure of the mRNA. A large segment immediately preceding the leader sequence was also removed in one of these mutants, ruling out generation of the 5' end of the mRNA via initiation of transcription at this point. The circularization of linear infecting DNA producing the DNA of the deletion mutants proceeded mainly by way of blunt end ligation in vivo. (29 refs)

- 79-5794 Transcription of Nucleosomal DNA in SV40 Minichromosomes by Eukaryotic and Prokaryotic RNA Polymerases. (Eng) Meneguzzi, G. (Centre de Biochimie, Faculté des Sciences, 06034 Nice, France); Chenciner, N.; Milanese, G. *Nucleic Acids Res* 6(8): 2947-2960; 1979.

Simian virus 40 (SV40) minichromosomes extracted from virions were transcribed with eukaryotic RNA polymerase B and with *Escherichia coli* RNA polymerase. With both RNA polymerases, transcription of minichromosomes was approx 25%-30% that of 'naked' SV40 superhelical DNA after 30 min of synthesis. Thus, for both eukaryotic and prokaryotic enzymes the presence of nucleosomes on the viral DNA did not completely inhibit transcription. Sedimentation analysis demonstrated that the size of RNA made on minichromosomes by either polymerase was smaller than the corresponding RNA made on deproteinized superhelical DNA. The av size reduction was from 1,500 to 1,000 nucleotides with *E. coli* polymerase and from approx 1,200 to 900 nucleotides with calf thymus RNA polymerase B. It is suggested that both RNA polymerases can transcribe portions of minichromosomal DNA that include a few nucleosomes. It is shown that minichromosome structure is not substantially altered by transcription by using (³H-thymidine)-labeled SV40 minichromosomes which were transcribed with *E. coli* RNA polymerase into ³²P-labeled RNA. Nascent RNA chains were only found associated with minichromosomes that had a full complement of nucleosomes. When tritium-labeled 'naked' SV40 superhelical DNA was used as the template, it was shown that RNA chains on the complex were precursors to those found in the major, slow sedimenting RNA peak. When SV40 minichromosomes or an

equivalent amount of deproteinized superhelical SV40 DNA was transcribed in vitro with *E. coli* or calf thymus B RNA polymerases, it was shown that with *E. coli* RNA polymerase, the fraction of RNA which became RNase resistant after self-hybridization was over 30% in the case of minichromosomes, as compared with 15% when 'naked' DNA was transcribed. Thus, a marked reduction in strand selectivity is imposed by nucleosomes on transcription with the prokaryotic enzyme. The poor strand selectivity exhibited by the eukaryotic enzyme was not improved when minichromosomes were used as template instead of 'naked' DNA. (30 refs)

- 79-5795 Sequence Heterogeneity at the 5' Termini of Late Simian Virus 40 19S and 16S mRNAs. (Eng) Canaani, D. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Kahana, C.; Mukamel, A.; Groner, Y. *Proc Natl Acad Sci USA* 76(7): 3078-3082; 1979.

In an attempt to identify the promoter for simian virus 40 (SV40) late transcription, the 5'-capped oligonucleotides of SV40 late 19S and 16S messenger RNA's (mRNA's) were examined. The 5'-capped leader sequence of the most abundant 19S and 16S mRNA's was previously mapped between 0.67 and 0.76 map units. In these studies, the two late mRNA species were found to contain multiple 5' ends. Eight different RNase T2-resistant cap structures were identified: m⁷GpppmAmpU (47%); m⁷GpppmAmpUmpU (19%); m⁷GpppmAmpC (16%); m⁷GpppmAmpCmpA (5%); m⁷GpppmAmpG (6%); m⁷GpppGmpC (3%); m⁷GpppmAmp-GmpA (2%); m⁷GpppGmpCmpG (2%). Capped T1 oligonucleotides of 19S and 16S mRNA's were isolated by two different procedures: (1) chromatography on a diethylaminoethylcellulose column followed by paper electrophoresis and (2) two-dimensional electrophoresis/homochromatography. Cap structures of the isolated 5' oligonucleotides were identified. Each of the major caps was found to be associated with a few different 5' oligonucleotides, implying a vast heterogeneity at the termini of SV40 late mRNA's. The results suggest that on SV40 DNA, RNA polymerase II has a repertoire of initiation points. In most of the cases, initiation takes place with ATP followed by a pyrimidine. Alternatively, transcription may start at one specific point, but a unique mechanism of processing generates heterogeneous populations of termini with a common 5'-ATP. (41 refs)

- 79-5796 Identification and Mapping of N⁶-Methyladenosine-containing Sequences in Simian Virus 40 RNA. (Eng) Canaani, D. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Kahana, C.; Lavi, S.; Groner, Y. *Nucleic Acids Res* 6(8): 2879-2899; 1979.

To learn more about the functional role of internal methylated residues, sequences containing N⁶-methyladenosine (m⁶A) were identified and compared in simian Virus 40 (SV40) nuclear and messenger RNA (nRNA and mRNA) and in host cellular mRNA. The av number of M⁶A oligonucleotides in SV40 16S and 19S mRNA's was determined, and the methylated sequences were localized on the viral genome. Late SV40 16S and 19S mRNA's contained an av of three MA residues/mRNA molecule. In both viral and cellular mRNA's, the methylated residues occurred in either Gpm⁶ApC or (Ap)m⁶ApC RNA sequences, where n = 1-4. More than 60% of the m⁶A residues in SV40 16S and 19S mRNA's were in Gpm⁶ApC sequences, despite there being twice as many (A)nAC than GAC sequences in these mRNA's. In the 16S

mRNA, two of the m⁶A residues were at the 5' coding region between 0.95 and 0.0 map units; the third residue mapped between 0.0 and 0.14 map units in the translated portion of the mRNA. The methylation pattern of the 19S mRNA was similar, although some differences between the 16S and 19S mRNA's were observed in the content and localization of the longer (AP)/m⁶ApC sequences. These results provide the first example of the precise localization of internal methylation sequences in mRNA species with defined coding specificity. The results imply that (1) localization of m⁶A residues is not random but rather specific to a particular region of the RNA; (2) apart from sequence specificity, other structural features of the mRNA may influence internal methylation, and (3) m⁶A residues are present in coding regions of SV40 mRNA's. (39 refs)

- 79-5797 Survival of Apurinic SV40 DNA in the D-complementation Group of Xeroderma Pigmentosum. (Eng) Kudrna, R. D. (Dept. of Biochemistry, Univ. California, Berkeley, CA 94720); Smith, J.; Linn, S.; Penhoet, E. E. *Mutat Res* 62(1): 173-181; 1979.

The survival of depurinated form I simian virus 40 (SV40) DNA was measured in normal human fibroblasts and in D-complementation xeroderma pigmentosum (XP) fibroblasts by an infective center assay. Heat-acid treatment and methyl methanesulfonate (MMS) were used as depurinating agents. After 3 hr of depurination by heat-acid treatment, infectivity in normal cells was <15% of the control levels, compared with >50% for the XP cells. Similar results were obtained with MMS-treated DNA. These results are contrary to expectation, since apurinic endonuclease activity, which is presumed to be involved in the repair of apurinic sites, is much lower in XP D-cell strains than in normal cell strains. The results indicate that there may be another mechanism for the repair of apurinic sites. (34 refs)

- 79-5798 Relationship Between Single-stranded DNA Isolated from Mouse Cells Transformed by Simian Virus 40 and Transcription of Cellular and Virus Genes. (Eng) Shaoof, D. (Laboratoire de Biologie Moléculaire, Groupe de Recherche No. 8, C.N.R.S., Institut Gustave-Roussy, 94800 Villejuif, France); Hanania, N.; Harel, J.; May, E. *J Gen Virol* 43(3): 571-581; 1979.

The relationship between single-stranded DNA (ssDNA) isolated from SV-3T3 mouse cells nonproductively transformed by simian virus 40 (SV40) and transcription of cellular and viral genes was investigated. A minor fraction of ssDNA was isolated by an improved method of hydroxyapatite chromatography (HAC) from the native nuclear DNA (nDNA) of SV-3T3 cells. Molecular hybridization, monitored by the use of S₁ nuclease, HAC, isopycnic centrifugation, and thermal melting, showed that ssDNA from SV-3T3 cells (which amounts to 1.5%-2% of the total nDNA) has the same characteristics as ssDNA previously isolated from other cell species. Only 27%-28% of the SV-3T3 ssDNA reassociated with itself, but the majority reassociated with the nonrepetitive portion of nDNA and up to 38% hybridized to homologous RNA. Only 7%-8% of bulk nDNA hybridized to homologous RNA. Highly radioactive virus probes (SV40-³H-complementary RNA synthesized in a cell-free system and the separated early and late strands of SV40 DNA labeled with ³²P) were annealed to different excess amounts of cellular DNA. Each probe hybridized at saturation levels, and the various reaction kinetics indicated that ssDNA is greatly enriched in virus sequences, mainly those originating from the early DNA strand, which is predominantly expressed in SV-3T3 cells. (27 refs)

- 79-5799 Persistence of Phage λ DNA in Genomes of Mouse Cells Transformed by λ-carrying SV40 Vectors. (Eng) Muzyczka, N. (Dept. Immunology and Medical Microbiology, Univ. Florida, Gainesville, FL 32610). *Gene* 6(2): 107-122; 1979.

Experiments aimed at establishing methods for incorporating foreign DNA into the chromosomal DNA of mammalian cells are described. To test the suitability of simian virus 40 (SV40) DNA as a vector for inserting DNA segments into the chromosomes of mammalian cells, an *Eco*RI-A fragment of bacteriophage λ DNA was covalently joined to a fragment of SV40 DNA and used to transform BALB/c 3T3 mouse cells in culture. Three independent, morphologically transformed clones were obtained that were positive for SV40 tumor (T) antigen by immunofluorescence staining. DNA from each transformant was examined by restriction enzyme analysis and found to contain both λ and SV40 sequences. Comigration of some fragments containing λ and SV40 sequences following digestion of transformed cell DNA by each of four different restriction enzymes indicated that part of the retained λ and SV40 DNA was linked in two of the three lines. In the third line, however, none of the restriction fragments had both λ and SV40 sequences. Although the presence of nonintegrated λ DNA was not excluded, at least some of the λ DNA appeared to be linked to host cell DNA. The results of digestion by *Eco*RI suggested that in some cases, the transforming linear molecule had probably circularized prior to integration. (37 refs)

- 79-5800 Simian Virus 40 Recombinants Are Produced at High Frequency During Infection with Genetically Mixed Oligomeric DNA. (Eng) Wake, C. T. (Marrs McLean Dept. Biochemistry, Baylor Coll. Medicine, Houston, TX 77030); Wilson, J. H. *Proc Natl Acad Sci USA* 76(6): 2876-2880; 1979.

A strategy for increasing simian virus 40 (SV40) recombination by bypassing the inefficient intermolecular step is described. Oligomeric SV40 was constructed in vitro by ligation of mixtures of pairs of linear DNA's carrying genetically distinct temperature-sensitive (ts) mutations. Cultured monkey cells infected with the unfractionated ligation products yielded frequencies of nonparental recombinant progeny that were increased up to 500-fold relative to cells infected with a mixture of the untreated circular molecules. Pairwise crosses were performed with tsB4, tsB8, and tsBC11 DNA's, using unfractionated oligomers constructed from linear molecules cleaved by *Eco*RI or *Bam*HI. In each cross, the fraction of progeny with nonparental genotypes was roughly proportional to the physical distances between the mutant sites. These results suggest a random, rather than site-specific, conversion of oligomers to monomers. Somewhat surprisingly, nonligated mixtures of linear tsB4 and tsB8 DNA's, created by *Eco*RI digestion, produced a 40- to 100-fold increase in the frequency of nonparental progeny. These results indicate that intermolecular associations must occur with fairly high efficiency between these linear molecules. (26 refs)

- 79-5801 Protein Kinase Activity Associated with Simian Virus 40 T Antigen. (Eng) Griffin, J. D. (Sidney Farber Cancer Inst., Boston, MA 02115); Spangler, G.; Livingston, D. M. *Proc Natl Acad Sci USA* 76(6): 2610-2614; 1979.

The results of experiments designed to assess whether any of the simian virus 40 (SV40) tumor (T) antigens have protein kinase activity are reported. Incubation of SV40 (T) antigen-containing immunoprecipitates with [γ -³²P]ATP resulted in the incorporation of

radioactive phosphate into large T antigen. Highly purified preparations of large T antigen from a SV40-transformed cell line, SV80, were able to catalyze the phosphorylation of a known phosphate acceptor, casein. The kinase activity migrated with large T antigen through multiple purification steps. Sedimentation analysis under non-T-antigen-aggregating conditions revealed that kinase activity and the immunoreactive protein comigrated as a 6S structure. The kinase activity of purified preparations of large T antigen could be specifically adsorbed to solid-phase anti-T IgG, and partially purified T antigen from a SV40 temperature-sensitive tsA transformant was thermolabile in its ability to phosphorylate casein when it was compared with comparably purified wild-type T antigen. These observations indicate that SV40 large T antigen is closely associated with protein kinase (ATP:protein phosphotransferase) activity. (47 refs)

- 79-5802 Intracellular Forms of Simian Virus 40 Nucleoprotein Complexes. II. Biochemical and Electron Microscopic Analysis of Simian Virus 40 Virion Assembly. (Eng) Coca-Prados, M. (Rockefeller Univ., New York, NY 10021); Hsu, M. T. *J Virol* 31(1): 199-208; 1979.

The simian virus 40 virion assembly process was studied with pulse-labeling kinetics of virion proteins, CsCl gradient analysis, electron microscopy, and low-salt gel electrophoresis. The results obtained are consistent with the model of gradual addition and organization of capsid proteins around simian virus 40 chromatin. Empty virions, as previously observed in the CsCl gradient, were found to be the dissociation product of immature virus. Histone H1 was found in simian virus 40 chromatin and virion assembly intermediates but not in the mature virion banding at 1.34 g/ml in the CsCl gradient. (21 refs)

- 79-5803 Biology of Simian Virus 40 (SV40) Transplantation Antigen (TrAg). V. In Vitro Demonstration of SV40 TrAg in SV40 Infected Nonpermissive Mouse Cells by the Lymphocyte Mediated Cytotoxicity Assay. (Eng) Pretell, J. (Dept. Pathology, Yale Univ. Coll. Medicine, New Haven, CT 06520); Greenfield, R. S.; Tevethia, S. S. *Virology* 97(1): 32-41; 1979.

The development of simian virus 40 (SV40)-specific transplantation antigen (TrAg) on the surface of nonpermissive mouse cells infected with SV40 was demonstrated in vitro using a sensitive, lymphocyte-mediated, ⁵¹Cr-release cytotoxicity assay. The assay was specific for the detection of SV40 TrAg. The antigen was detected 24 hr after infection of mouse cells with SV40, and high levels of TrAg expression persisted for as long as 96-120 hr after virus infection. The development of TrAg on the surface of the infected cells correlated with the synthesis of tumor antigen in nucleus. The synthesis and expression of TrAg on the surface of these cells may be an important step in the development of cell-mediated type immunological resistance in an SV40-inoculated host, leading to the elimination of stably transformed cells. (27 refs)

- 79-5804 Concanavalin A-mediated In Vitro Activation of Lymphocytes Primed Against Syngeneic SV40-induced Tumor-associated Antigens in Mice into Secondary Effector Cells Capable of Specifically Preventing Tumor Growth. (Eng) Glaser, M. (Dept. Biochemistry, George Washington Univ. Medical Center, 2300 I St., N.W., Washington, DC 20037). *Cell Immunol* 46(1): 201-207; 1979.

Spleen cells from female BALB/c mice immunized against a syngeneic simian virus 40 (SV40)-induced tumor, mKSA, prevented specifically the growth of the corresponding tumor in a tumor cell neutralization assay following preincubation of the cells for 5 days with mitogenic concentrations of concanavalin A (Con A). This reactivity was T-cell-dependent, independent of remaining Con A, and was detected at least up to 60 days following in vivo antigenic immunization. A similar reactivity was obtained with mitogenic concentrations of phytohemagglutinin but not with the B-cell mitogen lipopolysaccharide. Since this reactivity was indistinguishable from that obtained upon in vitro secondary antigenic stimulation with SV40-transformed cells, it is suggested that activation of precytotoxic cells against a syngeneic tumor by Con A into cytotoxic cells may be mediated by the same or similar receptors triggered by the stimulating tumor-associated antigens. (17 refs)

- 79-5805 Lysosome Stability during Lytic Infection by Simian Virus 40. (Eng) Einck, K. H. (Dept. Microbiology, Univ. Massachusetts, Amherst, MA 01003); Norkin, L.C. *Intervirology* 12(1): 47-56; 1979.

CV-1, LLC-MK₂, and BALB 3T3 cells infected with simian virus 40 (SV40) were studied to determine whether their lysosomes ruptured prior to cell death. As indicated by trypan blue staining, 40% to 80% of the CV-1 cells had undergone irreversible injury by 48 hr postinfection. However, as indicated by staining with acridine orange or neutral red, the lysosomes were intact at 24 and 48 hr postinfection. In some of the infected cells, the neutral red-stained lysosomes appeared to be grossly swollen. All of the cells containing such lysosomes were able to exclude trypan blue. Acid phosphatase activity was localized in discrete cytoplasmic particles at 48 hr, as indicated by histochemical staining of both fixed and unfixed cells. The results suggest that impaired membrane metabolism plays an important role in cell killing by SV40. (21 refs)

- 79-5806 SV40-related T-Antigen Expression in Human Meningiomas with Normal and G-22-monosomic Karyotype. (Eng) May, G. (Institut für Humangenetik, Universität des Saarlandes, 6650 Hamburg, W. Germany); Fischer, H.; Zang, K. D. *J Gen Virol* 43(3): 697-700; 1979.

Meningioma cell cultures were analyzed for the presence of nuclear fluorescence specific to simian virus 40 (SV40) tumor (T) antigen by the indirect immunofluorescence technique. Six of 16 meningiomas tested in early subculture showed SV40 T antigen. Two different antisera specific for T antigen were used: one gave a positive reaction with six tumors, and the other gave a positive reaction with only two tumors. In one T-antigen-positive meningioma, the typical nuclear fluorescence changed, beginning with the second subculture, into an unusual brilliant granular pattern that was irregularly distributed over the nuclei. In six meningiomas, a specific chromosome aberration (monosomy G 22) was established. However, up to now, no clear correlation between karyotype and T-antigen expression could be found: cells from three meningiomas with positive reactions had normal karyotypes, whereas those from three tumors with monosomy G 22 showed no T antigen. (8 refs)

- 79-5807 Vp1 Affects Intracellular Localization of Vp3 Polypeptide During Simian Virus 40 Infection. (Eng)

Kasamatsu, H. (Dept. Biology, Univ. California at Los Angeles, 405 Hilgard Ave., Los Angeles, CA 90024); Nehorayan, A. *Proc Natl Acad Sci USA* 76(6): 2808-2812; 1979.

To understand the functions of simian virus 40 (SV40) genes, the effect of temperature-sensitive (ts) mutations on the localization of viral antigens after infection was studied. Permissive cells (TC7) were infected with SV40 mutants ts in the complementation groups A, B, C, BC, and D at permissive and nonpermissive temperatures. Cells were examined for the localization of viral polypeptide antigens by immunofluorescent staining with monospecific antibodies. (1) The appearance of Vp1 antigen in cells infected by tsB, C, or BC mutants was not affected appreciably by the mutations. (2) The appearance of Vp3 antigen was affected by mutations in B, C, or BC. Vp3 antigen is confined to the nuclei in cells infected by wild-type virus. With mutant virus infection, Vp3 antigen is found in the cytoplasm, perinuclear region, and nucleoli. (3) The tsD mutants and the tsA mutants did not express either Vp1 or Vp3 antigens at the nonpermissive temperature. (4) Nucleoli seem to play an essential role in the biosynthesis and assembly of viral polypeptides. Thus, mutations in any one of complementation groups B, C, or BC, which are within the structural gene for Vp1, alter the intracellular distribution of another late gene product, Vp3. These results suggest that the amino acid sequences of Vp1 polypeptide play a role(s) in the transport of viral antigens across internal membranes and/or in virus assembly. (29 refs)

79-5808 Studies on Tumor-associated Antigens of Sarcoma Induced by Calf Adenovirus Type 3 and by Human Adenovirus Type 12 in Hamsters. (Bul) Bashkaev, I. S. (P.A. Gertsen Moscow Scientific Res. Inst. Oncology, Moscow, USSR); Ageenko, A. I.; Silianovska, K.; Boeva, M. *Onkologiya* 16(1): 32-34; 1979.

The tumor-associated antigens of sarcomas induced by calf adenovirus type 3 (sarcoma A-3) and human adenovirus type 12 (sarcoma A-12) in hamsters were studied by gel immunodiffusion. Complete serological identity of the two sarcomas was determined. The antigens contained by the two tumors were very similar, which was demonstrated by the fact that their precipitation lines coincided. In both cases, these antigens were present in the tumors only. The findings indicate the similarity of the two adenoviruses. (9 refs)

79-5809 Mutations that Allow Human Ad2 and Ad5 to Express Late Genes in Monkey Cells Map in the Viral Gene Encoding the 72K DNA Binding Protein. (Eng) Klessig, D. F. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY 11724); Grodzicker, T. *Cell* 17(4): 957-966; 1979.

The isolation of five independent host-range mutants (Ad2hr400-hr403, Ad5hr404) of human adenovirus serotype 2 and 5 (Ad2 and Ad5) that overcome the block to growth of wild-type adenovirus in monkey cells and form plaques and multiply efficiently in monkey and human cells is reported. The alteration in each of these mutants allowed the full expression of all viral late genes, in marked contrast to the depressed synthesis of many late proteins in monkey cells infected with the parental Ad2 or Ad5. The altered gene encoded a diffusible product, since the mutation acted in trans to enhance the synthesis of wild-type Ad3 late proteins during co-infections of monkey cells with Ad2hr400 and Ad3. Restriction enzyme analysis of the genomes of all the host-range mutants

showed that none contained major alterations. The mutation responsible for the extended host range was physically mapped by marker rescue experiments using isolated restriction enzyme fragments of the mutants to transfer the new phenotype to wild-type adenovirus. The alteration in each of the five mutants was located in a region (coordinates 62-70.7; coordinates 62-68 for Ad5hr404) that encodes predominantly the 72K DNA binding protein. More detailed mapping using Ad2hr400 fragments placed the mutation entirely within the 72K. (38 refs)

79-5810 Isolation and Characterization of a Specific Deletion Mutant of Human Adenovirus Type 2. (Eng) Van Roy, F. (Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium); Engler, G.; Fiers, W. *Virology* 96(2): 486-502; 1979.

A specific deletion mutant of human adenovirus type 2 (dl-Ad2), detected when pools of wild-type Ad2 were grown at a high multiplicity of infection in HeLa cells, was isolated and characterized. dl-Ad2 was enriched when the defective Ad2-simian virus 40 (SV40) hybrids of the Ad2**HEY population were cloned in monkey cells in the presence of an added excess of wild-type Ad2. Electron microscope heteroduplex analysis and restriction endonuclease examination established the Ad-specific nature of the dl-Ad2 DNA and revealed a single, homogeneous deletion of about 0.08 to 0.09 fractional genome length situated between 0.78 and 0.87 Ad2 map units. This genome structure is very similar to that of several other incomplete adenoviruses described previously. The deleted segment encompasses one of the four early genome regions of Ad2. dl-Ad2 particles are not infectious in both human and monkey cells, although the mutant DNA is replicated in these cell types. dl-Ad2 is able to interfere efficiently with SV40 DNA replication in coinfecting monkey cells. Furthermore, virus populations consisting exclusively of Ad2**HEY hybrid viruses and dl-Ad2 "helper" viruses can be cloned, indicating that dl-Ad2 can complement sufficiently for the large Ad2 DNA deletion in the Ad2**HEY hybrid genomes. (42 refs)

79-5811 Multiple Discrete Sites for Premature RNA Chain Termination Late in Adenovirus-2 Infection: Enhancement by 5,6-Dichloro-1- β -D-ribofuranosylbenzimidazole. (Eng) Fraser, N. W. (Wistar Inst., 36th St. at Spruce, Philadelphia, PA 19104); Sehgal, P. B.; Darnell, J. E. *Proc Natl Acad Sci USA* 76(6): 2571-2575; 1979.

The oligonucleotide composition of short adenovirus 2 (Ad2)-specific RNA that accumulates late in infection is described. Discrete-sized short RNA chains that contained the distinctive oligonucleotides, including the 5'-capped oligonucleotide, characteristic of the first 600 nucleotides of the Ad2 large, late, rightward-reading transcriptional unit (16.4-99) accumulated in Ad2-infected HeLa cells. In the presence of 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole, the accumulation of these chains was enhanced, as was the accumulation of short chains from a neighboring rightward-reading transcriptional unit (3.0-10.7). These short chains appeared to represent prematurely terminated transcripts. Late in infection, there was a marked increase in RNA synthesis, including that of prematurely terminated short chains, from the large late transcriptional unit. This suggests that the increase in transcription and messenger RNA production from this region late in infection is not due to reduced "attenuation" of RNA synthesis. (35 refs)

79-5812 Affinity of Oncogenic Adenoviruses for Lysosomes in Infected Cells. (Eng) Ogier, G. (Unite de Virologie Fondamentale et Appliquee, INSERM, Groupe de Recherche 33 1/m CNRS, 1, Place de Professeur Joseph Renaut, 69371 Lyon Cedex 2, France); Gazzolo, L.; Lyon, M.; Chardonnet, Y. *Microbios Lett* 8(31/32): 133-137; 1978.

The distribution of virus particles in various cell compartments during penetration of adenoviruses (Ad) 4 and 31 into HeLa cells was studied, and the results are presented together with those of previously reported similar studies of Ad 1, 4, 5, 7, 12 and 31. Ad 7, 31 (both subgroup B), and 12 (subgroup A) are oncogenic for newborn hamsters, while Ad 1 and 5 (subgroup C) are not. Ad 4 (subgroup C) is not oncogenic but shares many features with subgroup B serotypes. Electron microscopic examination 30-120 min following infection of HeLa cells with Ad 4 or Ad 31 at 10-100 plaque-forming units (PFU)/cell demonstrated that 32%-44% of these viral particles were sequestered in the lysosomes, thus demonstrating that there are quantitative differences in Ad particle sequestration in lysosomes for the different serotypes; 5%-10% sequestration has been reported for Ad 1 and 5, while 65%-82% has been demonstrated for Ad 7 and 12. These results indicate that viral particles nononcogenic for newborn hamsters have a higher capacity to release into the cytoplasm from the phagocytosing vacuoles before their fusion with lysosomes. Most of the oncogenic particles do not escape from the phagocytosing vacuoles and are found trapped in the lysosomes, where they remain infectious. It is suggested that the passage of oncogenic serotypes through lysosomes might be a necessary step for the expression of their transforming ability. (13 refs)

79-5813 Pre-Early Adenovirus 5 Gene Product Regulates Synthesis of Early Viral Messenger RNAs. (Eng) Berk, A. J. (Dept. Microbiology, LSB 5034, Univ. California, Los Angeles, CA 90024); Lee, F.; Harrison, T.; Williams, J.; Sharp, P. A. *Cell* 17(4): 935-944; 1979.

The S1 nuclease gel technique was used to examine the expression of early messenger RNA (mRNA) after infection of HeLa cells with adenovirus 5 host range (Ad5) hr group I and II mutants. The Ad5 hr group II mutants stimulated the synthesis of a wild-type pattern of early mRNAs. In contrast, infection of HeLa cells with Ad5 hr group I mutants gave rise to only two early mRNAs, which mapped from 1.5-4.4 units, or in the same region as the Ad5 hr group I mutants. Since infection of HeLa cells with Ad5 hr group I mutants was defective for synthesis of cytoplasmic mRNAs complementary to three early regions in the right half of the genome and to the early region 4.5-11.0 units, nuclear RNA from these cells was also analyzed for the presence of precursor RNA chains using the S1 nuclease gel technique. Nuclear precursors were not detected in Ad5 hr group I-infected HeLa cells, suggesting that the gene product defective in these mutants is required by synthesis of stable nuclear RNA from the three early regions in the right half of the genome and from the early region 4.5-11.0 units. (52 refs)

79-5814 Location of Additional Early Gene Sequences in the Adenoviral Chromosome. (Eng) Galos, R. S. (Dept. Biological Sciences, Carnegie-Mellon Univ., Pittsburgh, PA 15213); Williams, J.; Binger, M. H.; Flint, S. J. *Cell* 17(4): 945-956; 1979.

Regions in the type C human adenovirus (Ad) genome expressed during the early phase of productive infection were studied using

marker-rescue and hybridization techniques. Ad5 DNA-terminal protein complex was used to infect 293 cells, and mutant DNA-protein complex was used in marker rescue. The H5ts36, H5ts149, and H5ts69 mutations were mapped between 18.5 and 22.0 units on the Ad5 genome; all three early ts mutants are classified within complementation group N. Saturation hybridization experiments revealed in the Ad2 genome two sets of I strand sequences to the left of position 26.5 units that are complementary to early cytoplasmic RNA. RNA sequences complementary to the IVa₂ gene were located on the 8.0-17.0-unit fragment, and four units of the I strand were located between 18.5 and 23.24 units. Early cytoplasmic RNA was fractionated on oligo(dT)-cellulose columns, and the Ad sequences complementary to different single-stranded DNA probes were assayed. RNA sequences hybridizing to the two I strand regions above included some carrying poly(A). The RNA sequences complementary to the I strand between 11 and 14 units and between 19.8 and 23.24 units were calculated to be present at concentrations of about 20 and 30 copies/cell, respectively. Experiments in which HeLa cells were infected at unequal input multiplicities with Ad5 wild-type and temperature-sensitive mutants suggested that the H5ts36 gene codes for a product, possibly of catalytic function, which is either present or required at a very low level early in infection. (53 refs)

79-5815 Phenotypic Properties and Tumor Promoter-induced Alterations in Rat Embryo Cells Transformed by Adenovirus. (Eng) Fisher, P. B. (Div. Environmental Sciences, Inst. Cancer Res., Coll. Physicians and Surgeons Columbia Univ., 701 W. 168th St., New York, NY 10032); Goldstein, N. I.; Weinstein, I. B. *Cancer Res* 39(8): 3051-3057; 1979.

The phenotypic properties of seven clones of secondary rat embryo cells (SREC) transformed by a temperature-sensitive mutant of human adenovirus type 5 (H5ts125) were analyzed to determine whether transformants obtained from cultures treated with a chemical carcinogen prior to virus infection had a different phenotype than those obtained from cultures treated with virus alone. The effects of prolonged serial passage and the effects of exposure of the clones to 12-O-tetradecanoylphorbol-13-acetate (TPA) on the expression of several markers of transformation were also determined. Compared with normal SREC, most of the transformants had a reduced population-doubling time, increased saturation density, reduced serum requirement, increased plasminogen activator production, reduced large external transformation-sensitive protein, increased lectin agglutinability, and decreased anchorage dependence (ie, growth in agarose and agar). Prolonged serial passage of the transformants led to a spontaneous increase in cloning efficiency in agar. There was no consistent difference between the phenotypes of transformants obtained from cultures treated with carcinogen plus virus or those of transformants obtained with virus alone, although the former transformants appeared to express anchorage independence at earlier subpassages. The most striking finding was that TPA appreciably enhanced the growth in agar of all transformants. Two early passage-transformed clones grew in agar only in the presence of TPA. The tumor promoter also increased the saturation densities and enhanced the cloning efficiencies in liquid medium of most of the transformants. These effects were not seen with normal SREC. These results suggest that following adenovirus transformation, there is a spontaneous progression in the expression of markers of transformation and that phorbol ester tumor promoters can accelerate this process. (45 refs)

79-5816 Cleavage Maps of Weakly Oncogenic Human Adenovirus Type 7 DNA by Restriction Endonuclease

BamHI and SalI. (Eng) Yoshida, K. (Dept. Molecular Biology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan); Sekikawa, K.; Fujinaga, K. *Tumor Res (Sapporo)* 13: 14-19; 1978.

Weakly oncogenic human adenovirus type 7 DNA (Grider strain) was cleaved into 10 and 3 specific fragments by the restriction endonucleases *BamHI* and *SalI*, respectively. These specific fragments were mapped on the adenovirus type 7 genome by analyzing the partial digestion products and by DNA-DNA hybridization. (12 refs)

79-5817 Analysis of Human Cancer DNA's for DNA Sequences of Human Adenovirus Serotypes 3, 7, 11, 14, 16, and 21 in Group B. (Eng) Wold, W. S. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63110); Mackey, J. K.; Rigden, P.; Green, M. *Cancer Res* 39(9): 3479-3484; 1979.

Molecular hybridization with highly radioactive adenovirus 7 (Ad7) or adenovirus 11 (Ad11) DNA was used to analyze 125 human cancer DNA's and 37 normal tissue DNA's for Group B Ad sequences. Hybridization of Ad7-radiolabeled DNA with DNA's from an Ad7-induced primary hamster tumor and from two cell lines (5728 and Ad7 P-cell) established from Ad7-induced hamster tumors indicated that there were multiple copies per cell of 17%, 30%-36%, and 20%, respectively, of the Ad7 genome. No Ad7 sequences were detected in DNA's from 16 normal human lung tissues, 18 normal digestive tissues, 34 cancers of the respiratory system, 19 cancers of the digestive system, 11 cancers of the urinary system, 5 cancers of the genital system, 3 cancers of the breast, or 6 Hodgkin's lymphomas. No Ad11 sequences were detected in DNA's from 9 bladder carcinomas, 10 prostate carcinomas, 24 renal carcinomas, 3 renal cell carcinomas, 3 Wilms' tumors, or 2 normal kidneys. The data provide evidence but not formal proof that none of the human cancers analyzed were induced by Group B Ad's. (46 refs)

79-5818 Revertants of Adenovirus Type-12-transformed Hamster Cells Have Lost Part of the Viral Genomes. (Eng) Groneberg, J. (Inst. Genetics, Univ. Cologne, Cologne, W. Germany); Doerfler, W. *Int J Cancer* 24(1): 67-74; 1979.

Eighteen morphological revertants isolated from line T637, which was derived from BHK21 cells (subline B3) by transformation with adenovirus type 12 (Ad12), were characterized. The T637 cells were round and epithelioid, but the revertant cells were fibroblasts. The revertants arose spontaneously and could be enriched by letting the T637 culture grow to very high density. The T637 cells detached from the plastic surface, whereas the revertants stayed attached and could then be cloned. The morphological revertants differed from the B3 and T637 lines with respect to saturation density, growth rate, agglutinability by plant lectins, and uptake of low-mol-wt compounds. The revertants were all tumor-antigen negative, but they reacted with anti-LETS serum (antisera against the large, external, transformation-sensitive protein). The B3 and T637 cells were LETS-negative. The revertants exhibited a pseudodiploid karyotype. All 18 revertants could be transplanted into 4-wk-old Syrian hamsters, although most of them grew less rapidly than the B3 cells. The patterns of integration of Ad12 DNA were investigated by a DNA-DNA hybridization technique. Four of the revertant lines appeared to have lost almost all their viral DNA sequences; the other revertant lines

lacked several of the viral DNA sequences present in the T637 line, which contained multiple copies of the viral genome. Upon superinfection of all the lines with Ad2, Ad2 replication was inhibited in T637 cells, but Ad2 grew as efficiently or even more so in the revertants than in the B3 line. (19 refs)

79-5819 A Marsupial Oncovirus? (Eng) Hamilton, R. C. (Commonwealth Serum Lab., 45 Poplar Road, Parkville, Victoria 3052, Australia); MacGregor, A.; Pye, D. *J Gen Virol* 44(2): 535-539; 1979.

The development of a virus-like particle observed in two continuous cell lines derived from the marsupial, *Sminthopsis crassicaudata* (fat-tailed dunnart), was investigated. The development of the particle was similar to the development of D-type oncoviruses. Initially, a crescent of nucleoid material was observed near the nucleus in the region of the Golgi apparatus. This crescent developed into a doughnut-shaped A-type particle, which migrated through the cytoplasm toward the cell membrane, where it began to bud. Budding took place either into a cytoplasmic vacuole or from the cell membrane. The particle continued moving until it consisted of a circular knob connected to the cell by an isthmus of cytoplasm, which elongated and narrowed until the particle broke free from the cell. Only enveloped A-type particles were observed; no mature B-type, C-type or D-type particles were detected. (20 refs)

79-5820 Type C Virus and Immunoglobulin A Production by Murine Myeloma MOPC-315: Two Independent Activities. (Eng) Gazit, A. (Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ., Tel-Aviv, Israel); Yaniv, A.; Halperin, D.; Ben-Efraim, S. *Infect Immun* 25(2): 569-573; 1979.

The suspected correlation between cessation of type C virus production and cessation of immunoglobulin secretion by murine myeloma cells was studied using immunoglobulin A-producing (IAP) and -non-producing (NP) variants of the murine myeloma MOPC-315. Complementary DNA (cDNA) prepared from the virus particles released by NP cells was annealed at identical Crt values to 70S RNAs extracted from viral particles from both NP and IAP cells. Both RNA species followed the same hybridization kinetics curve and 87% final hybridization, suggesting that the nucleotide sequences of the viruses shared extensive homology. This homology was further substantiated by similar melting profiles and identical thermal stability values (approx 90°C). The two myeloma variants also released similar levels of virus particles. Cytoplasmic RNAs from both IAP and NP cells annealed to the same extent and with the same kinetics as cDNA prepared from NP virus, demonstrating that the viral genomes were equally transcribed in the two plasmacytomas. The data indicate that the amount of extracellular viral particles, as well as the level of viral gene expression occurring in the myeloma cells are not affected by the loss of cell capacity to secrete IgA protein. (23 refs)

79-5821 Characterization of a Type-C Virus Produced by Cocultures of Human Leukemic Bone-Marrow and Fetal Canine Thymus Cells. (Eng) Smith, R. G. (Lab. Tumor Cell Biology, NCI, Bethesda, MD 20014); Nooter, K.; Bentvelzen, P.; Robert-Guroff, M.; Harewood, K.; Reitz, M. S.; Lee, S. A.; Gallo, R. C. *Int J Cancer* 24(2): 210-217; 1979.

The putative human helper virus SKA-21/A204V, isolated in 1977 from human leukemic bone marrow cells following coculture with normal fetal canine thymus cells (Cf2th), was characterized with respect to its major viral core protein, reverse transcriptase, and nucleic acid sequences. The analyses show that this virus is closely related to the C-type woolly monkey virus simian sarcoma virus-1/simian sarcoma associated virus-1, but contains no detectable determinants, either genetic or immunologic, that are related to Rauscher murine leukemia virus or to the baboon endogenous virus M7. (52 refs)

pying poliovirus RNA, it was first purified by phosphocellulose chromatography and further purified 60-fold by poly(U)-Sephadex chromatography. The poly(U) polymerase activity copurified with the replicase activity. Although less-pure replicase fractions copied a variety of RNA's, purer fractions responded better to poliovirus RNA than to other viral RNA's. Even the less-pure fractions made a specific copy of the added template, as shown by hybridization of the product to its template RNA but not to other RNA's. Among homopolymers, only poly(A)-oligo(U) was copied by the replicase; other primed homopolymer templates were inactive. (23 refs)

79-5822 Poliovirus Replicase: A Soluble Enzyme Able to Initiate Copying of Poliovirus RNA. (Eng) Dasgupta, A. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA 02139); Baron, M. H.; Baltimore, D. *Proc Natl Acad Sci USA* 76(6): 2679-2683; 1979.

The soluble phase of the cytoplasm of poliovirus-infected HeLa cells contains an enzyme activity able to copy RNA without an added primer. This replicase activity is absent from uninfected cells. To determine whether this soluble, poliovirus-specific, poly(U) polymerase activity corresponds to an enzyme also capable of co-

See also:

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*(Chem.): 79-5626, 79-5640.

*(Phys.): 79-5687, 79-5693.

*(Immun.): 79-5825, 79-5829, 78-5836, 78-5837.

*(Path.): 79-5921.

*(Epid.-Biom.): 79-5943, 79-5954, 79-5959.

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- 79-5823** Correlation of Immunogenetic and Histological Changes in Immuno-deficient Mutant hr/hr Mice. (Eng) Reske-Kunz, A. B. (Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021); Scheid, M. P.; de Sousa, M.; Boyse, E. A. *Adv Exp Med Biol* 114: 55-58; 1979.

The number of cells expressing the Lyt-1 and Lyt-123 surface phenotypes was studied in HRS/J mice, which carry the hairless (hr) mutation associated with premature immunodeficiency and a higher incidence of leukemia. At approx 3-3.5 mo of age, hr/hr homozygotes showed a highly significant increase in Lyt-123 cells and an equally significant decrease in Lyt-1 cells, compared with age-matched, hr/+ littermates. These changes were paralleled by a scarcity of splenic germinal centers and the development of abnormal lymphoid cell aggregates. Further findings suggested that these changes also occurred in the heterozygotes at a later age. (6 refs)

- 79-5824** Prolongation of Survival Time of Mice Inoculated with Myeloid Leukemia Cells by Inducers of Normal Differentiation. (Eng) Honma, Y. (Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-362, Japan); Kasukabe, T.; Okabe, J.; Hozumi, M. *Cancer Res* 39(8): 3167-3171; 1979.

Studies were conducted to determine whether the leukemogenicity of sensitive mouse myeloid leukemia (M1) cells is affected by treatment with inducers of cell differentiation, whether resistant and sensitive M1 cells differ in immunogenicity, and whether the possible decrease of leukemogenicity caused by inducers can be separated from enhancement of T-lymphocyte-mediated immune responses. Inducers of cell differentiation [certain proteins, bacterial lipopolysaccharides (LPS), or glucocorticoids] significantly enhanced the survival times of inbred SL mice inoculated with sensitive cells, but they scarcely affected the survival times of mice inoculated with resistant cells. Some mice inoculated with the sensitive cells and treated with LPS did not develop leukemia. Sensitive and resistant clone cells contained similar common tumor-associated surface antigens. Treatment with LPS was also effective in athymic nude BALB/c mice inoculated with the sensitive M1 cells. LPS increased the survival times of these mice, which suggests that the inhibitory effect of LPS is not directly involved in T-lymphocyte-mediated immune responses. LPS and glucocorticoid significantly stimulated differentiation of the sensitive cells cultured in a diffusion chamber in vivo, but they had little effect on the differentiation of resistant cells. These results suggest the possibility of treating, with partial success, leukemia in vivo with differentiation inducers. (31 refs)

- 79-5825** Thymic Dependence of Cell-mediated Immunity to Avian Sarcomas in Chickens. Immunological Characterization of a Nonvirion Antigen in Virus-infected Cells. (Eng) Wainberg, M. A. (Lady Davis Inst. Medical Res., Jewish General Hosp., 3755 Cote Sainte Catherine Rd., Montreal, Quebec H3T 1E2, Canada); Beiss, B.; Wahi, R.; Israel, E. *Cell Immunol* 45(2): 344-355; 1979.

Cell-mediated immunity in chickens bearing tumors induced by avian retroviruses was studied in a peripheral lymphocyte stimulation assay. To determine whether virion or nonvirion antigen(s) elicited a blastogenic response, lymphocytes of normal and tumor-bearing chickens were exposed to supernatant fluids of avian retrovirus-infected chicken embryo fibroblast cells and to the plasma of birds that had been inoculated with avian myeloblastosis virus. The results indicated that the antigenic activity being measured was virus group specific, cell transformation independent, and nonvirion in nature. Paradoxically, the expression of such antigen(s) was restricted to cells that actively synthesized progeny avian retrovirus particles; it was absent in mammalian non-producer cells that had been transformed by avian sarcoma viruses. The ability to respond immunologically to such antigen(s) was present in birds inoculated with either leukosis or sarcoma viruses. Thymectomy, but not bursectomy, stimulated tumor growth and abolished the immune responsiveness of sensitized lymphocytes in this system. (36 refs)

- 79-5826** Production of Lymphoid Tumors in Hamsters by Direct Implantation of Human Umbilical Cord WBC. II. Analysis of Adenoma Structural Cells. (Jpn) Matsuda, Y. (Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan). *Acta Haematol Jpn* 42(3): 368-376; 1979.

Human umbilical cord WBC were transplanted intraarterially in newborn hamsters, and the resulting lymphoid tumor cells were separated into human and hamster cells and then subdivided by specific anti-human and anti-hamster rabbit sera. Human cells comprised approx 79.6% of the lymphoid tumor cells, and hamster cells 18.7%. Approx 23.3% of the human cells were erythrocyte rosette (ER)-forming T cells, 1.7% were human Ig-positive B cells, and the rest had neither of these two markers. The transformed cells that were anti-human serum-positive were divided into two main types: (1) ER-positive and Ig-negative, and (2) ER-negative and Ig-negative. A small number of these cells were also ER-negative and Ig-positive. Cells with both a negative and positive response were also found among the hamster cells. These results suggest that there is a correlation between lymph node enlargement and the graft-vs-host reaction. (26 refs)

- 79-5827** Origin Of Chronic Myelocytic Leukemia in a Precursor of Pre-B Lymphocytes. (Eng) LeBien, T. W. (Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, 420 Delaware St. SE, Minneapolis, MN 55455); Hozier, J.; Minowada, J.; Kersey, J. H. *N Engl J Med* 301(3): 144-147; 1979.

The malignant cells of three patients with Philadelphia chromosome-positive chronic myelocytic leukemia in blast crisis were characterized immunologically. The patients were three women, aged 41, 43, and 3 yr, respectively. Cells from all three patients were negative for the sheep RBC receptor, surface immunoglobulin, Fc receptors, and C3 complement receptors. However, all were positive for an "acute lymphoblastic leukemia-associated antigen" and human p23,30 (immune-associated antigen-like) antigen. Two patients were positive for cytoplasmic

IgM: the cells of one were also positive for cytoplasmic kappa chains, and the cells of the other were positive for cytoplasmic lambda chains. (23 refs)

- 79-5828 Subset Derivation of T-Cell Acute Lymphoblastic Leukemia in Man. (Eng) Reinherz, E. L. (Div. Tumor Immunology, Sidney Farber Cancer Inst., Boston, MA 02115); Nadler, L. M.; Sallan, S. E.; Schlossman, S. F. *J Clin Invest* 64(2): 392-397; 1979.

To determine whether human T-cell acute lymphoblastic leukemia (T-ALL) cells belong to one or another T-cell subset, cell-surface phenotyping was performed on tumor populations from 25 patients with T-ALL. Tumor cells from these 25 individuals were either TH₁ or TH₂, but not both. Five of 25 patients had TH₁ T-ALL cells. These TH₁ tumor populations were found exclusively in children and often without an accompanying thymic mass. TH₂ T-ALL, in contrast, occurred in both children and adults and was almost always associated with thymic enlargement. Although children with TH₁ T-ALL had as high or higher peripheral blast counts on presentation than their TH₂ T-ALL counterparts, overall survival was greater for the TH₁ group (>36 mo) than the TH₂ group (<12 mo). These studies demonstrate that T-cell leukemias in humans arise from distinct T-cell subsets and that cell-surface characterization of T-cell malignancies may provide useful clinical data related to prognosis. (39 refs)

- 79-5829 In Vivo Activity of Lymphocytes Sensitized in Vitro by Antigen-fed Macrophages: Inhibition by Lymphoma Growth. (Eng) Treves, A. J. (Dept. Radiation and Clinical Oncology, Inst. Oncology-Hadassah Univ. Hosp., Jerusalem, Israel); Feldman, M.; Honsik, C.; Kaplan, H. S. *Adv Exp Med Biol* 114: 629-634; 1979.

The possibility that effector lymphocytes induced in vitro by radiation leukemia virus (RadLV)-fed macrophages may affect tumor growth in vivo by recruitment of the host defense response was studied using specific pathogen-free (C57BL/Ka x BALB/c)F₁ mice. Spleen lymphocytes which had been sensitized by RadLV-fed macrophages were injected ip into normal mice 4 days prior to the injection of BL/VL₃ lymphoma cells. Compared with control lymphocytes, the sensitized lymphocytes protected against lymphoma growth. The 4-day time interval was required for this protective activity. Whereas irradiation of the lymphocytes did not affect their protective activity, irradiation of the recipient mice abolished the protective response. Spleen cells which had been sensitized directly against BL-5 cells (a noninfected line derived from C57BL/Ka embryo fibroblasts) protected recipient mice against tumor development; this protection was weaker than that conferred by macrophage-mediated sensitized lymphocytes and was completely abolished by irradiation of the sensitized cells. (13 refs)

- 79-5830 Tumor-specific Immunity Induced by Somatic Hybrids. II. Elicitation of Enhanced Immunity Against the Parent Plasmacytoma. (Eng) Kim, B. S. (Dept. Microbiology-Immunology, Northwestern Univ. Medical and Dental Schs., Chicago, IL 60611). *J Immunol* 123(2): 739-744; 1979.

Hybrid cells derived from the fusion of a BALB/c plasmacytoma (TEPC-15) and L cells (C3H origin) were used to stimulate tumor-

specific immunity against the parental plasmacytoma cells. Live hybrid cells induced tumor-specific immunity against TEPC-15 more effectively than mitomycin-treated hybrid or TEPC-15 tumor cells. Adoptive transfer of immunity with spleen cells of mice immunized with hybrid cells was also more effective than that with mitomycin-treated tumor cells. The immunity induced by the hybrid cells was specific to the TEPC-15 tumor, because the mice that received immune spleen cells were not protected against challenge with either HOPC-8 or McPC-603 plasmacytomas. T cells were primarily responsible for the transfer of specific immunity based on the sensitivity of immune cells to anti-Thy 1.2 and complement. Mice that had established solid tumors were treated with 5×10^7 spleen cells to evaluate the therapeutic value of the hybrid-induced immune cells. Tumors in mice that received immune cells gradually regressed over a 40-day period, whereas tumors in control mice continued to grow. These results suggest that a rearrangement of tumor-specific transplantation antigens on allogeneic hybrid cells can enhance their immunogenicity. (36 refs)

- 79-5831 Tumor-specific Immunity Induced by Somatic Hybrids. I. Lack of Relationship Between Immunogenicity and Tumorigenicity of Selected Hybrids. (Eng) Kim, B. S. (Dept. Microbiology-Immunology, Northwestern Univ. Medical Sch., Chicago, IL 60611); Liang, W.; Cohen, E. P. *J Immunol* 123(2): 733-738; 1979.

The morphology, tumorigenicity, and immunogenicity of three representative hybrid clones derived from the fusion of TEPC-15 plasmacytoma cells of BALB/c mice with L cells of C3H mice were compared. One clone (LTC-1) showed a morphology intermediate to that of either parental cell and possessed the highest tumorigenic and immunogenic properties. The other two clones displayed a flat morphology that differed significantly from that of either parent. One of these two, LTC-4, eventually induced tumors in some (BALB/c x C3H)F₁ mice but failed to stimulate protective immunity against TEPC-15 tumor cells in BALB/c mice. The other hybrid clone, LTC-2, had a very flat morphology and did not induce tumors, although it was capable of stimulating a significant level of tumor immunity. Histologically, all tumors induced by the hybrid cells were fibrosarcomas rather than plasmacytomas. These results indicate that the morphology of hybrid cells may be correlated with their tumorigenicity as well as with the histologic appearance of the tumors they produce. In addition, the degree of tumorigenicity of individual hybrid clones does not correspond to their immunogenicity in the host, suggesting that major antigens responsible for immunogenicity may not play an important role in tumor induction. (23 refs)

- 79-5832 Effect of Exposure to a Heterogeneous Adenocarcinoma on the Mineral Oil Induction of Plasma Cell Tumors in BALB/c Mice. (Eng) Harkonen, W. S. (Dept. Medicine, Univ. Minnesota Medical Center, Minneapolis, MN 55455); Theologides, A. *IRCS Med Sci (Cancer)* 7(6): 291; 1979.

Exposure to transplanted heterogeneous adenocarcinoma tissue increased the incidence of mineral oil-induced plasma cell tumors in BALB/cby mice. This effect appeared to be mediated whether the mice experienced actual growth of the transplanted tumor, or whether the graft was rejected. (6 refs)

- 79-5833 Release of Immature Cells from the Thymus During Solid Tumor Growth: Identification by Assay of TdT

Activity. (Eng) Small, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Lasser-Weiss, M.; Daniel, V. *J Immunol* 123(1): 259-262; 1979.

The hypothesis that as tumor growth progresses, early thymocytes (TC's) with tumor-enhancing activity are released from the thymus and accumulate in the periphery where they may counteract the activity of tumor-inhibiting T cells was tested. Experiments were undertaken to determine whether artificial introduction of TC's into the periphery can cancel tumor inhibition by sensitized spleen cells during the period when the splenocytes manifest antitumor reactivity and whether immature cells are naturally released from the thymus and accumulate in the spleen as tumor growth progresses and the antitumor response fades. Three groups of C3H/eb mice were challenged sc with 5×10^4 syngeneic fibrosarcoma cells plus: no additional treatment, 5×10^6 nucleated spleen cells from tumor-bearing mice in the tumor-inhibiting period, or 5×10^6 nucleated spleen cells from tumor-bearing mice during the tumor-inhibiting period that had been injected with TC's 24 hr earlier. Control mice received tumor cells alone. The spleen cells came from mice that had received 5×10^4 fibrosarcoma cells 3.5 wk before becoming spleen donors. The TC's were taken during repopulation of cortisone-depleted thymuses, 48 hr after injection of 5 mg hydrocortisone acetate into donor mice. Compared with controls, tumor growth was inhibited in mice receiving sensitized spleen cells, but the inhibiting activity was abolished by the injection of TC's. Thus, TC that reached the periphery by artificial means neutralized the activity of the tumor-inhibiting cells. To determine whether premature TC release occurs naturally, T cells usually found in the thymus and not in the spleen were identified by assaying for the thymus cell marker enzyme terminal deoxynucleotidyl transferase (TdT) in populations of TC's and spleen cells from normal or tumor-bearing C3H/eb mice, in both the tumor-inhibiting and tumor-enhancing periods. Significant TdT activity was observed in TC's but not in spleen cells from normal mice, it was found at a low level in spleen cells tested during the early tumor-inhibiting stage, and it was considerably elevated in spleen cells tested during the later tumor-enhancing stage. These results suggest that recently released TC's accumulate in the spleen during the progression of tumor growth in parallel with the gradual eclipse of antitumor reactivity in the spleen cells. (24 refs)

79-5834 Cell-mediated Immune Response to Syngeneic Ultraviolet-induced Tumors. II. The Properties and Antigenic Specificities of Cytotoxic T Lymphocytes Generated In Vitro Following Removal from Syngeneic Tumor-immunized Mice. (Eng) Daynes, R. A. (Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, UT 84132); Fernandez, P. A.; Woodward, J. G. *Cell Immunol* 45(2): 398-414; 1979.

The immune responses of C3Hf mice to syngeneic fibrosarcomas induced by UV light or methylcholanthrene (MC) were measured in vitro by the ability of cytotoxic T lymphocytes (CTL) from immunized animals to kill ^{51}Cr -labeled tumor targets in a 6-hr assay. The CTL were generated by the in vitro culturing of draining popliteal lymph node (DLN) cells derived from animals that were footpad immunized 8 days previously. CTL activity was generated using DLN cells from both normal (UV tumor-resistant and UV-exposed (UV tumor-susceptible) C3H mice. The kinetics of CTL generation between these two groups, however, was different in that the lymphocytes from normal animals appeared to differentiate into CTL faster than the lymphocytes from the UV-irradiated mice. The in vitro generation of CTL activity was found to be extremely radiosensitive and was also inhibited by the presence of viable tumor cells within the cell culture. Once generated, the CTL

were extremely insensitive to the effects of γ radiation. The CTL is a T lymphocyte that appears to be immune-associated antigen-negative. The CTL derived from mice immunized to syngeneic UV- or MC-induced tumors were capable of expressing cross-reactive non-major histocompatibility complex-restricted killing of multiple tumor targets. Cold cell inhibition experiments confirmed the presence of cross-reactive determinants on various tumors and also established the presence, within a single CTL preparation, of effector cells with specificity for both the unique tumor-specific transplantation antigens as well as the common (cross-reactive) tumor-associated antigens. (27 refs)

79-5835 Cytolytic Antibodies to Methylcholanthrene-induced Sarcomas Elicited by Immunization of Syngeneic Mice. (Eng) Merino, F. (Dept. Experimental Medicine, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela); Abeyounis, C. J.; Milgrom, F. *Eur J Cancer* 15(6): 829-835; 1979.

The specificity of the antibodies produced by immunizing syngeneic animals with chemically induced tumors and the reported cross-reactivity of these tumors with tumors of different histogenetic origin, such as lymphomas, were analyzed. Cytolytic antibodies were tested in the sera of C3H/HeHa mice grafted twice with a solid syngeneic methylcholanthrene (MC)-induced sarcoma or immunized with an ascitic form of the MC sarcoma. These sera reacted with syngeneic tumor cells as well as with normal and malignant allogeneic cells. Absorption experiments suggested that the antisera contained two populations of antibodies. One population combined with antigen(s) shared by the MC sarcomas of C3H/HeHa mice, the normal and malignant cells of C3H/St mice, and the normal and malignant cells of C57BL/6 mice. The other antibody population failed to react with the cells of C57BL/6 mice, but it reacted with C3H/HeHa MC sarcoma cells and with normal and malignant cells of C3H/St origin. (24 refs)

79-5836 Induction of Transplantation Resistance with Soluble Simian Virus 40-induced Hamster Tumor-specific Transplantation Antigen. (Eng) Coggin, J. H. (Univ. South Alabama, Coll. Medicine, Dept. Microbiology and Immunology, Mobile, AL 36688). *Cancer Res* 39(8): 2952-2959; 1979.

Multiple injections of 3 M KCl extracts of simian virus 40 (SV40)-induced Syrian golden hamster sarcoma cells did not inhibit tumor growth in syngeneic hamsters following homologous tumor challenge. When a single injection of this extract was administered in the range of 0.5 mg of antigen protein, tumor appearance was delayed significantly, and a significant number of challenge animals failed to develop tumors in two of three experiments. A single injection of the tumor cell extract generally conferred to 20%-40% permanent protection, always with a marked delay in tumor appearance. The immunity was specific in that immunization with normal muscle extracts or heterologous tumor challenge did not protect against or delay tumor appearance. Higher or lower amounts of homologous, soluble tumor transplantation antigen given in a single injection were either without effect or promoted tumor development. The resistance observed in animals receiving a single dose of soluble tumor antigen could only be detected if the hamsters were challenged with 5×10^6 tumor cells. Challenge with only 10^4 tumor cells did not lead to the detection of resistance. The immunity induced by a single optimal dose of tumor antigen could be transferred to normal, uninjected hamsters at 20 days postsensitization with lymph node cells, but not with

peritoneal exudate cells from injected donors, suggesting that the immunity detected in animals immunized with soluble tumor extracts was cell-mediated. These data indicate that antigen dose, regimen of administration to the host, and the challenge level used to detect transplantation resistance are all important parameters to consider when using cell-free, tumor-associated transplantation antigens. They strongly support and extend an earlier report derived in another model with a chemically induced tumor. (28 refs)

- 79-5837 Role of Regional and Distant Lymph Nodes in Rejection of Feline Sarcoma Virus-induced Tumors in Sheep. (Eng) Theilen, G. H. (Dept. Surgery, Section Clinical Oncology, Sch. Veterinary Medicine, Univ. California, Davis, CA 95616); Pedersen, N. C.; Higgins, J. *J Natl Cancer Inst* 63(2): 389-400; 1979.

The sequential immunologic responses that occur over a 30- to 40-day span in lymph nodes regional and distant to feline sarcoma virus (FeSV)-induced tumors were investigated in nine crossbred Corridale sheep. Following injection of FeSV-transformed allogeneic or autochthonous fibroblasts into the lower leg, small tumors developed at the site of inoculation and subsequently regressed. Efferent lymph from the regional popliteal nodes and distant nodes in the same host was collected for periods up to 40 days after tumor cell inoculation. The cell response in the efferent lymph of the stimulated node was the same regardless of whether the inoculum consisted of autochthonous or allogeneic FeSV-transformed sheep cells. There was a rapid rise in total lymphocytes leaving the regional node, beginning at 3 days and peaking at 6-8 days postinoculation. On days 6-8 postinoculation, lymphoblasts ranging from 25% to 40% of the total cell output appeared in the regional lymph. The cell population in lymph from distant (nonstimulated) nodes, however, remained morphologically normal throughout the response. Lymphocytes cytotoxic to the injected FeSV-transformed cells appeared in efferent lymph from the regional node within 5 days postinoculation and in lymph from distant nonstimulated nodes several days later. Cytotoxic lymphocytic cells had no killing effect against the corresponding non-transformed cells if the inoculum was autochthonous in origin; however, they did have such an effect when corresponding non-transformed cells were allogeneic. The cytotoxicity of the lymph cells varied according to the type of cells in the lymph. With the use of the growth inhibition assay, it was possible to demonstrate that lymph cell populations high in lymphoblasts killed all target cells in 24 hr, whereas populations of lymph cells comprised mainly of small lymphocytes took up to 2-3 days to kill the target cells. Complement-dependent antibody first appeared in lymph from the stimulated popliteal node at 8 and 12 days postinoculation in blood sera and lymph from distant nodes. (29 refs)

- 79-5838 Immunological Status of Patients Bearing Benign and Malignant Neoplasia. (Eng) Kudesia, M. (Dept. Pathology, Lady Hardinge Medical Coll., New Delhi, India); Malik, G. B. *Indian J Cancer* 15(3): 59-62; 1978.

The immunological status of 32 patients with malignant neoplasms (MN), 10 patients with benign neoplasms (BN), and 10 healthy controls was studied. Of the MN patients, 62.5% were tuberculin-negative, compared with only 10% in the BN and control groups. All MN patients with Stage I neoplasms were tuberculin-positive, whereas all with Stage IV neoplasms were negative. Blast transformation of lymphocytes was greatly reduced in the MN (24.92%) patients compared with the BN (51.00%) and control (52.17%)

subjects ($p = 0.0005$). The mean transformation index of the tuberculin-positive MN patients was 45.48%, compared with only 10.95% in the tuberculin-negative MN patients. Total serum proteins did not differ significantly between the MN and other subjects, but the concentration of serum globulin was significantly higher in the MN group than in the other two groups ($p = 0.0005$). (11 refs)

- 79-5839 Microspectrofluorometric Analysis of Surface Antigens of Murine Melanoma and Hamster Peritoneal Cell Hybrids: Comparisons of Species Antigenicity, Chromosome Number, and Tumorigenicity. (Eng) Erickson, K. L. (Dept. Human Anatomy, Sch. Medicine, Univ. California, Davis, CA 95616); Hu, F. *Oncology* 36(3): 101-104; 1979.

The surface antigenicity, karyotype, and tumorigenicity of somatic cell hybrids formed by the fusion of murine melanoma (PAZG) x Chinese hamster peritoneal cells (CH) were compared. One line, F57-(9), which arose from the hybridization of two CH cells and one PAZG cell, had slight (6%) CH chromosome loss but 80% PAZG chromosome loss after 10 mo in culture. These cells expressed CH antigens strongly and PAZG antigens weakly. In comparison, another hybrid, F57-(7), formed from one CH and one PAZG cell, lost 20% of its chromosomes after 10 mo in vitro. These cells had a stronger expression of PAZG antigens and a weaker expression of CH antigens than F57-(9). These findings indicate a direct relationship between chromosome number and antigenicity; tumorigenicity, however, does not appear to depend on the chromosome numbers of the parental cells. (25 refs)

- 79-5840 Pyoderma Gangrenosum and IgG Paraproteinemia. (Ger) Zabel, M. (Dermatologische Klinik und Poliklinik, Universitat Essen--GHS, Hufelandstrasse 55, D-4300 Essen, W. Germany); Brandle, I. *Med Klin* 74(10): 358-360; 1979.

The case report of a 68-yr-old patient with pyoderma gangrenosum and IgG paraproteinemia with kappa-type light chains is presented. The paraproteins that are observed in pyoderma gangrenosum without overt myeloma could represent early symptoms of plasmacytoma. (14 refs)

- 79-5841 The Distribution and Localization of Immunoglobulin in the Gastric Mucosa and Gastric Cancer. (Eng) Ohta, Y. (First Dept. Internal Medicine, Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo, Japan); Kino, I.; Kato, Y.; Aoyama, Y. *Acta Pathol Jpn* 29(4): 523-531; 1979.

The distribution and localization of immunoglobulin (Ig) in specimens of gastric mucosa, intestine, and gastric cancer were studied by immunofluorescence techniques. The gastric mucosa specimens were taken from stomachs with various degrees of chronic gastritis. Specimens of intestine were taken from cancer patients, but the tissue was removed far from the localized lesions, and it was histologically normal. IgA-producing cells predominated in the lamina propria of the stomach and in other regions of the gastrointestinal tract; in the stomach, however, the population density of all kinds of Ig-producing cells, especially those producing IgA, was more variable from case to case than that in the intestine. In metaplastic gastric mucosa, all IgA-, IgM-, and IgG-producing cells were reduced equally. In the intestine,

there was an even distribution of cells containing IgA and secretory component (SC: dimeric IgA bound with epithelial glycoprotein) in the glandular epithelium. In normal gastric mucosa, only a limited number of glands contained IgA and SC, mainly in the deep foveolar epithelium. However, almost all the glands in gastric metaplasia specimens contained IgA and SC. The distribution of IgA and SC was similar to that in the intestine. There were two interesting findings in the gastric cancer tissues: (1) 2/20 differentiated and 7/22 undifferentiated cancers were stained with anti-IgA and anti-SC antiserum. Thus, some gastric cancer cells retained the ability to produce SC and they took up IgA in their cytoplasm. In the differentiated cells, the specific fluorescence was present apically, whereas in the undifferentiated cells, it was distributed diffusely in the cytoplasm. (2) In one case of undifferentiated cancer, many IgG-producing inflammatory cells were observed in and around the cancer tissue. (21 refs)

- 79-5842 Hermans' Syndrome and Gastric Cancer. (Fre) Ram-pal, P. (Centre d'Hepato-gastro-enterologie, Avenue Reine Victoria 4, F-06000 Nice, France); Karsenty, C.; Prieur, J.; Vedel, J. P.; Delmont, J. *Acta Gastroenterol Belg* 42(3/4): 150-158; 1979.

A 64-yr-old woman developed a gastric adenocarcinoma as the last manifestation of late-onset immunoglobulin deficiency associated with nodular lymphoid hyperplasia of the ileum (Hermans' syndrome). The patient was admitted to the hospital in January 1973 with chronic diarrhea without fever or vomiting. There was no abdominal or arthritic pain. Immune studies showed very low levels of IgG and almost no IgM and IgA. Delayed hypersensitivity reactions to dinitrochlorobenzene and tuberculin were negative. The percentages of T and B lymphocytes were normal, but lymphoblast transformation tests were negative. The diarrhea failed to respond to medical treatment, and arthritic pain appeared in October 1973. A cancer of the antrum of the stomach was observed upon barium transit x-ray and endoscopy. Surgery in December 1973 revealed localized gastric cancer. Literature reports on gastrointestinal cancer in immune-deficient patients are briefly reviewed. (29 refs)

- 79-5843 The Effect of BCG Immunotherapy on the Kinetic Parameters and Growth Curves of Five Transplantable Colon Carcinoma Lines Chemically Induced in the Rat. (Fre) Martin, M. S. (Laboratoire d'Immunologie, Faculte de Medecine 7, Bd Jeanne-d'Arc, F 21033 Dijon, France); Martin, F.; Justrabo, E.; Michel, M. F.; Lagneau, A. *Gastroenterol Clin Biol* 3(3): 247-253; 1979.

The growth effects of two intratumoral injections of BCG were evaluated in five transplantable colon carcinoma lines induced by 1,2-dimethylhydrazine in BD-IX rats. Tumor fragments weighing 45-90 mg were implanted in the anterior of the rat thorax. As soon as the transplanted tumor measured 0.5 cm, the rats were inoculated intratumorally with BCG (2 0.5-ml doses of a 9-g/liter NaCl soln); control rats were inoculated intratumorally with NaCl. Of the total 165 grafts, 106 were successful. Several tumor growth parameters were measured and compared in the 51 rats inoculated with BCG and the 55 controls: length of survival, tumor volume, and metastases in animals with progressively growing tumors, doubling time, time required for the tumor to obtain a volume of 1 cm³, and the exponential growth curves following the Gompertz model. Although there were significant differences in the growth parameters among the five cell lines, BCG did not significantly alter tumor growth. (15 refs)

- 79-5844 Lymphocytes, Neutrophils and Serum Immunoglobulins in Patients with Precancerous States of the Larynx. (Eng) Gieriek, T. (Dept. Laryngology, Silesian Acad. Medicine, Francuska Str. 20/24, Katowice, Poland); Lisiewicz, J.; Astaldi, G.; Pilch, J. *Laryngoscope* 89(7, part 1): 1145-1150; 1979.

The lymphocyte and neutrophil cytochemistry and serum immunoglobulin levels were evaluated in 24 men aged 32 to 58 yr with precancerous states of the larynx, ie, leukoplakia, papillomas, and pachydermia. The peripheral blood lymphocytes were cytochemically stained for N-acetyl- β -glucosaminidase (AGA), β -glucuronidase (GU), acid phosphatase, and glycogen and the neutrophils were stained for alkaline phosphatase, myeloperoxidase, and lipids. The results were expressed in terms of absolute counts of positive cells and of the activity index score. IgG, IgA, and IgM levels were also determined. The results were compared with those in 20 healthy men aged 20-30 yr. The patients exhibited elevated numbers of AGA- and GU-positive lymphocytes. A characteristic feature was an increase in the absolute counts of lymphocytes with diffuse and granular-diffuse types of cytochemical reactions for all enzymes studied. The number of cells with the granular type of reaction (intact enzyme-positive lysosomes) was significantly reduced. These cytochemical alterations were accompanied by a significant increase in the serum IgA level. These results are discussed with reference to the response of the lymphoid system to tissues of precancerous lesions of the larynx. With respect to the neutrophils, the patients exhibited a significant intracellular decrease in GU activity and a decrease in lipid levels, as well as elevated alkaline phosphatase activity. The GU deficiency may be significant in the diminished cytotoxic response of the neutrophils against the tumor and precancerous lesion cells. (10 refs)

- 79-5845 Evaluation of the PHA Skin Test in Patients with Lung Cancer, Pulmonary Tuberculosis, and Leprosy. (Jpn) Kado, M. (Second Dept. Medicine, Chest Disease Res. Inst., Kyoto Univ., Kyoto, Japan); Kitaichi, M.; Matsui, Y.; Izumi, T.; Oshima, S.; Asamoto, H.; Motoaki, O. *Bull Chest Dis Res Inst Kyoto Univ* 12(1/2): 28-35; 1979.

The relationship between the immunological response of lung cancer patients to phytohemagglutinin (PHA) or purified protein derivative (PPD) and the types and stages of the disease was studied. Nine controls, 27 pulmonary tuberculosis patients, 14 leprosy patients, and 45 primary lung cancer patients (13 with squamous cell carcinoma, 17 with adenocarcinoma, 6 with small cell anaplastic carcinoma, and 9 with large cell anaplastic carcinoma; 9 Stage I, 5 Stage II, 21 Stage III, 10 Stage IV) were studied. Patients were inoculated sc with 5 μ g PHA or id with 0.05 μ g PPD in 0.1 ml saline and checked 24 or 48 hr later. In the PHA test, the av comparative diameter of the erythemas of the controls and the tuberculosis, lung cancer, and leprosy patients was 38.1, 31.2, 28.8, and 13.8 mm, respectively. The erythema diameter was 30.8, 32.4, 29.1, and 24.7 mm for the Stage I, II, III, and IV lung cancer patients, respectively. Low reactivity rates were generally seen in patients with small cell anaplastic carcinoma. The overall PPD reaction in the lung cancer patients was 62.8% of normal. A positive correlation between the PPD and the PHA reactions was observed in 27/43 lung cancer patients tested. No changes in the levels of RBC, WBC, glutamic pyruvic transaminase, lactate dehydrogenase, blood urea nitrogen, and lymphocytes were seen before or after the PHA test. There was a decreased immunological reaction in the later stages of lung cancer, as judged by the immunological responses of the hosts to the PHA test. (16 refs)

79-5846 Neoplasma and Kidney Transplants. Study at the Kidney Transplantation Unit of the Maisonneuve-Rosemont Hospital. (Fre) Archambault-Couture, L. (Departement de Medecine, Hopital Maisonneuve-Rosemont, Universite de Montreal, Quebec, Canada); Beaudry, C.; Legresley, L. P.; Laplante, L. *Union Med Can* 108(6): 681-684; 1979.

Three kidney transplant patients who developed a reticulosarcoma of the cerebellum, a hypernephroma, and a Wilms' tumor, respectively, are described. These three neoplasms were the only ones observed among a series of 179 kidney transplants performed in 162 patients during 1968-1978. The Wilms' tumor, which occurred in a 22-yr-old woman, is believed to be the first one to develop after a kidney transplant. (8 refs)

79-5847 Loss of Strain Specificity of the TA3-St Subline: Evidence for the Role of Epiglycanin in Mouse Allogeneic Tumor Growth. (Eng) Cooper, A. G. (Dept. Pathology, Tufts Univ. Sch. Medicine, Boston, MA 02111); Codington, J. F.; Miller, D. K.; Brown, M. C. *J Natl Cancer Inst* 63(1): 163-169; 1979.

The in vivo conversion of the standard strain-specific ascites murine mammary adenocarcinoma subline TA3-St to a new subline, TA3-MM, is reported. While TA3-St is neither allogeneically transplantable nor epiglycanin-bearing, the new subline did bear epiglycanin and grew in allogeneic mice in this study. The simultaneous acquisition of these two properties strongly suggests the role of epiglycanin in allogeneic tumor growth. (21 refs)

79-5848 Isolation and Partial Characterization of an Epiglycanin-like Glycoprotein from a New Non-Strain-specific Subline of TA3 Murine Mammary Adenocarcinoma. (Eng) Codington, J. F. (Lab. Carbohydrate Res., Massachusetts General Hosp., Boston, MA 02114); Cooper, A. G.; Miller, D. K.; Slayter, H. S.; Brown, M. C.; Silber, C.; Jeanloz, R. W. *J Natl Cancer Inst* 63(1): 153-161; 1979.

The detection, isolation, and partial characterization of an epiglycanin (EGC)-like glycoprotein (gp) from a new non-strain-specific ascites subline of the TA3 mammary adenocarcinoma TA3-MM are described. The subline, which arose in vivo from the strain-specific TA3-St subline during an acute respiratory illness of the syngeneic A/HeHa hosts, possessed at its surface a gp not found on the parent TA3-St cell. This gp, termed TA3-MM EGC, was characterized by a high mol wt (500,000), by potent inhibition of hemagglutination by the *Vicia graminea* lectin, and by carbohydrate and amino acid compositions nearly identical to those of the EGC gp present on the surface of the allotransplantable TA3-Ha ascites cell. Under the electron microscope, TA3-MM EGC present appeared as long extended rods with widths [2.5 nanometers (nm)] and lengths (450-500 nm) similar to those of TA3-Ha EGC. Incubation of each of two sublines of the TA3-MM ascites cell, TA3-MM/1 and TA3-MM/2, with modified trypsin followed by column chromatography produced approx 1.0- and 0.2-fold as much EGC-like material, respectively, as was obtained from the TA3-Ha ascites cell. Continuous growth of the TA3-MM cell in suspension culture resulted in an almost complete disappearance of EGC in a manner demonstrated earlier for the TA3-Ha cell grown under similar conditions. Allotransplantability in the TA3-MM cell may be due, at least in part, to the masking of histocompatibility antigens by EGC-like molecules. (30 refs)

79-5849 A Study of Host Defence Reaction of Breast Carcinoma and its Correlation with Generalised Delayed Hypersensitivity. (Eng) Nagar, R. (Dept. Pathology and Surgery, Lady Hardinge Medical Coll. and Hosp., New Delhi, India); Maheshwari, H. B.; Mukerjee, P.; Mittal, M. M. *Indian J Cancer* 15(3): 63-68; 1978.

Twenty-six patients with breast carcinoma (BC), 20 patients with benign breast neoplasms (BBN), and 20 normal, age-matched controls were studied for delayed hypersensitivity reactions and host defense reactions. In the controls and BBN group, a positive reaction to the tuberculin sensitivity test was achieved with 5 or 10 units of tuberculin. Fifteen of the BC patients responded to 5 units, 7 responded to 10 units, 2 responded to 100 units, and 2 did not respond. Two peaks of induration were observed in 75% of the normal controls after id injections of 2.5 million lymphocytes (NLT test). No reaction was observed within 10 days in 8/26 BC patients, only one peak was observed in 5 patients, two normal peaks were observed in 12 patients, and two abnormal peaks were observed in 1 patient. Contact sensitivity to dinitrochlorobenzene (DNCB) was induced in 20 BC, 20 BBN, and 15 control cases. A poorer response of the lymphoreticuloendothelial (LR-E) cells in and around the tumor and draining lymph nodes was observed in patients with advanced BC. The maximum depression of delayed hypersensitivity was observed in patients with Stage IV malignancy. The status of delayed hypersensitivity based on the tuberculin, DNCB, and NLT tests correlated with the LR-E reaction. (20 refs)

79-5850 Assessment of Cell Immunity in Precancerous Stages and in Carcinoma of the Cervix. (Ita) Bolis, P. F. (Cattedra di Patologia Ostetrica e Ginecologica, Universita degli Studi di Pavia, Pavia, Italy); Polatti, F.; Zara, C. *Minerva Ginecol* 31(6): 445-447; 1979.

Erythrocyte (E)-rosette formation was studied in 19 patients with moderate cervical dysplasia, 12 with carcinoma in situ (CIS) of the cervix, and 16 with invasive cervical carcinoma. E-rosette formation in the dysplasia and CIS patients was comparable to that observed in controls (45.5%, 51.2%, and 50.4%, respectively), but it was reduced significantly in patients with invasive carcinoma (31.9%). It is suggested that the neoplasia is initially controlled by the cell-mediated immunity of the host and that it becomes invasive when this immunity proves insufficient. (11 refs)

See also:

*(Rev.): 79-5455, 79-5459, 79-5460, 79-5461, 79-5462, 79-5463, 79-5464, 79-5465, 79-5467, 79-5469, 79-5470, 79-5471, 79-5472.

*(Chem.): 79-5547, 79-5552, 79-5630, 79-5632, 79-5639, 79-5670.

*(Viral): 79-5702, 79-5704, 79-5723, 79-5724, 79-5725, 79-5731, 79-5742, 79-5743, 79-5744, 79-5746, 79-5761, 79-5769, 79-5783, 79-5785, 79-5787, 79-5803, 79-5804, 79-5820.

*(Path.): 79-5863, 79-5867, 79-5884, 79-5908, 79-5914, 79-5915.

*(Epid.-Biom.): 79-5944, 79-5954.

PATHOGENESIS

- 79-5851 Measurement of Chromosomal Breakage in Cultured Cells by the Micronucleus Technique. (Eng) Heddle, J. A. (Dept. Biology, York Univ., Downsview, Toronto, Ontario M3J 1P3, Canada); Benz, R. D.; Countryman, P. I. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 191-196; 1978.

A series of experiments are reported in which chromosomal breakage in cultured cells was measured by the micronucleus technique. One of the consequences of chromosomal breakage is the production of micronuclei, and the number of micronuclei present in cells depends upon the extent of chromosomal breakage as well as other factors. The main advantage of measuring the micronuclei rather than the chromosomal aberrations directly is that the sampling time is greatly reduced since the technique is faster and requires less expertise. The main disadvantage is that even though the aberration frequency is constant, the frequency of micronuclei varies with the rate of cell division and the proportion of cells that divide. A miniature blood culture is set up in a microtube. The standard sampling time is 96 hr after the culture is begun. One slide is made per culture, and 500 cells from it are scored. The micronuclei are scored, even if three or more occur in the same cell, provided that there is a distinct main nucleus which is rounded rather than deeply lobulated. Data are presented from use of the test with normal lymphocyte cultures exposed to x-rays (400 R); with cultures from Down's syndrome donors and normal diploid donors irradiated at varying doses; with normal lymphocytes exposed to 400 R x-rays given in two 200 R fractions; with lymphocytes from control, Fanconi's anemia and Bloom's syndrome donors and their heterozygotes; with lymphocytes from Fanconi's anemia and control patients after mitomycin C was added at varying doses to the culture; and with ataxia telangiectasia and control fibroblast lines after anoxic γ -irradiation. Provided that the limitations of this assay are recognized, it can be a useful measure of chromosome breakage. (18 refs)

- 79-5852 Human Chromosomes Which Affect Tumorigenicity in Hybrids of Diploid Human with Heteroploid Human or Rodent Cells. (Eng) Klinger, H. P. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY); Baim, A. S.; Eun, C. K.; Shows, T. B.; Ruddle, F. H. *Cytogenet Cell Genet* 22(1-6): 245-249; 1978.

A study was conducted to determine if chromosomes (CS's) of human diploid (HD) cells can influence the tumorigenicity, in nude mice, of heteroploid human or rodent cells when introduced into the latter by cell fusion. Three series of hybrids between normal HD and heteroploid HPRT-deficient cells of human (D98AH2), Chinese hamster ovary (K627), and mouse (A9) origin were made, and a set of hybrids was selected from each series so that nearly all human CS's were represented in each set. Intraspecific hybrids that retained most of the CS's of the nontumorigenic diploid parent were also nontumorigenic. Preliminary results from the interspecific HD x rodent crosses showed that no human CS in single copy appears to be able to greatly affect tumorigenicity, since nearly all human CS's were represented at least once in cells of the

resulting tumors. This was also true for about 130 combinations of different CS's taken two at a time. However, many hybrids, particularly those with many human CS's, required higher cell inocula or longer periods of time to form tumors than heteroploid parental lines. CS's 8, 9, 11, 13, and 17 conveyed characteristics to cells that reduced their tumorigenic potential. However, the data are not extensive enough to rule out the possibility that other combinations of human CS's may have similar effects. In the HD x D98AH2 and HD x K627 series, the anchorage-independent and tumorigenic phenotypes did not fully correlate, since some hybrids able to grow in semisolid medium were not able to form tumors. However, a quantitative relationship may exist between these phenotypes, since most of the nontumorigenic hybrids had low plating efficiencies and grew slowly in semisolid medium, and the tumorigenic hybrids and the cells of their tumors generally grew quickly and plated at much higher efficiencies in this medium. The data are not compatible with the view that extrachromosomal elements intervene in the suppression of tumorigenicity, although this possibility is difficult to rule out. (8 refs)

- 79-5853 A Possible Association of Pernicious Anemia with Neoplasia. (Eng) Arvanitakis, C. (Dept. Medicine, Univ. Kansas Medical Center, Rainbow Blvd. at 39th St., Kansas City, KS 66103); Holmes, F. F.; Hearne, E. *Oncology* 36(3): 127-129; 1979.

To obtain further information on the incidence of neoplasms in pernicious anemia (PA), 39 PA patients (20 women, 19 men) seen at one institution over a 20-yr period were studied. Seven of the patients developed nine different neoplasms 3-20 yr after the diagnosis of PA. These primary neoplasms originated from the lymph nodes, larynx, colon, stomach, kidney, meninges, maxillary sinus, and eighth nerve. Treatment with vitamin B₁₂ did not influence tumor development. Statistical analysis showed that the observed incidence of nine neoplasms in this group was significantly higher than the expected 3.3 cases during the aggregate follow-up period ($p = 0.002$). Although a higher incidence of neoplasms in patients with other underlying diseases does not necessarily indicate an association, a high degree of suspicion for neoplastic disease is justifiable in PA patients. (15 refs)

- 79-5854 Familial Hodgkin's Disease: Case Report and Literature Review. (Ger) Hofer, H. O. (Medizinische Universitätsklinik Göttingen, Robert-Koch-Strasse 40, D-3400 Göttingen, W. Germany); Nagel-Studer, E.; Nagel, G. A. *Onkologie* 2(3): 113-118; 1979.

Malignant lymphoma [3 cases of Hodgkin's disease (HD), 1 case of reticulum cell sarcoma] developed in 4/5 sisters; two cases were diagnosed in 1962-1964 and two in 1971. The sisters who developed malignancies had similar immune response patterns, and these differed from the pattern of the healthy sister. This observation, plus a review of the literature on familial HD, are consistent with the view that an external agent plus inherited susceptibility are involved in HD. (85 refs)

79-5855 Chronic Myelomonocytic Leukemia Associated with Hereditary Pyruvate Kinase Deficiency and Multiple Acquired Erythrocyte Abnormalities. (Eng) Vives-Corrons, J. L. (Postgraduate Sch. Hematology 'Farreras Valenti', Hospital Clinico y Provincial, Univ. Barcelona, c/ Casonova, 143 Barcelona, Spain); Florensa, L.; Muncunill, J.; Nomdedeu, B.; Rozman, C. *Acta Haematol (Basel)* 61(3): 168-174; 1979.

A congenital RBC pyruvate kinase (PK) deficiency was found in a 72-yr-old woman with chronic myelomonocytic leukemia (CMML). The PK deficiency was associated with an increase in the RBC activity of hexokinase, 6-phosphogluconate dehydrogenase, and glutathione peroxidase and with a decrease in the activity of acetylcholinesterase, glutathione reductase, and glucosephosphate isomerase. The enzymatic abnormalities were accompanied by alterations in hemoglobin and in the i antigen content of the RBC membrane. In addition, bone marrow ultrastructural studies showed dyshemopoietic changes in all blood cell precursors and especially in erythroblasts. These findings confirm the close relationship between CMML and acquired dyserythropoietic syndromes, and they may help to clarify the nature of the rare association of hereditary PK deficiency with leukemia. (53 refs)

79-5856 Chronic Myelogenous Leukemia with Reticulum-Cell-Sarcoma-like Cell Proliferation. (Eng) Koide, O. (Dept. Pathology, Univ. Occupational and Environmental Health, Sch. Medicine, 1-1 Iseigaoka, Yahata, Nishi-ku, Kitakyushu 807, Japan); Watanabe, Y. *Acta Pathol Jpn* 29(4): 585-595; 1979.

A case of chronic myelogenous leukemia (CML) associated with a proliferation of atypical cells resembling those of reticulum cell sarcoma (RCS) is presented. The patient, a 41-yr-old man, presented with a short history of palpitation and general fatigue. Anemia, splenomegaly, and leukocytosis were discovered upon admission, and a diagnosis of CML was made. Approx 2.5 yr later, he was readmitted with acute crisis of CML, and he died soon thereafter. Histologic studies revealed the presence of several immature eosinophils intermingled with ordinary leukemic cells that had infiltrated the bone marrow, lymph nodes, spleen, liver, lungs, and testes. RCS-like cells either formed solitary nodular foci or they intermingled randomly with infiltrating leukemic cells. Charcot-Leyden crystals were seen in some areas where RCS-like cells proliferated. Eosinophilic granules were present in some of the RCS-like cells. They proved to be an immature form of specific granules of eosinophils, as evidenced by their staining properties and ultrastructural aspects. These results favor the view that the RCS-like cells are transformed leukemic cells of myelogenous origin. (25 refs)

79-5857 The Skin in Myelomonocytic Leukemia. (Ita) Carlesimo, O. A. (Clinica Dermatologica, Univ. Roma, Rome, Italy); Calvieri, S.; Chimenti, S.; Pala, S.; Bertana, C. *Chronica Dermatol* 9(6): 631-636; 1978.

A case of myelomonocytic leukemia with skin manifestations occurred in a 72-yr-old man. The patient presented with a 6-mo history of papular skin lesions that covered almost the entire body, particularly the trunk, face, and arms. No abnormalities were found on physical examination except a moderately enlarged liver. Blood tests revealed $3,200,000 \text{ RBC/mm}^3$, $3,000 \text{ WBC/mm}^3$ (70% lymphocytes, 18% blast cells), and an elevated IgG level. Tests for the Philadelphia chromosome were negative. Cytologically, large round cells with large, hyperchromic, centrally located nuclei

predominated. Occasionally, nucleoli were present. The cytoplasm was abundant and slightly basophilic. Histological examination of the skin lesions revealed essentially the same type of cell (large, round, monomorphic cells with large hyperchromic nuclei and an occasional nucleolus); however, the cytoplasm was eosinophilic. These cells were also prevalent in the bone marrow. Electron microscopic examination of ultrathin sections of the leukemic cells demonstrated numerous electron-dense granular vesicles in the cytoplasm. The patient was diagnosed as having myelomonocytic leukemia with skin infiltrations. (15 refs)

79-5858 The Hypophysis and Hemoblastoses. (Ger) Buchmann, E. (Pathologisches Institut der Ernst-Moritz-Arndt-Universität, Friedrich-Loeffler-Strasse 23e, DDR-22 Griefswald, E. Germany); Schwesinger, G. *Zentralbl Neurochir* 40(1): 35-42; 1979.

Among a series of autopsies of 165 patients with hemoblastoses, 38 cases of infiltration of the hypophysis were found. The highest incidence of hypophyseal infiltration was found among the lymphoblastic leukemias (3/9), followed by 18/62 cases of non-Hodgkin's lymphoma, 16/76 cases of myeloblastic leukemia, and 1/18 cases of Hodgkin's disease. (27 refs)

79-5859 Acute Nonlymphocytic Leukemia. Expression in Cells Restricted to Granulocytic and Monocytic Differentiation. (Eng) Fialkow, P. J. (Medical Service, Veterans Admin. Medical Center, 4435 Beacon Ave. S., Seattle, WA 98108); Singer, J. W.; Adamson, J. W.; Berkow, R. L.; Friedman, J. M.; Jacobson, R. J.; Moehr, J. W. *N Engl J Med* 301(1): 1-5; 1979.

Two patients (a 29-yr-old woman and a 2.5-yr-old girl) with acute nonlymphocytic leukemia who were heterozygous for the X-chromosome-linked enzyme glucose-6-phosphate dehydrogenase were studied to determine the number and type of cells in which the disease arises. Both type A and B isoenzymes were found in normal tissues, but the myeloblasts showed only one enzyme type, indicating that at the time of the study, the disease had a clonal origin. The observation in one patient that erythroid cells did not arise from this clone contrasts with conclusions reached in patients previously studied with chromosome markers. The results suggest that in this patient, the leukemic clone suppressed the expression of normal granulopoiesis but did not inhibit erythroid differentiation from normal progenitors. They suggest also that the disease is heterogeneous. In some patients, the disease is expressed in cells with differentiation restricted to the granulocyte-macrophage pathway; in others, it involves stem cells that also differentiate into RBC. This heterogeneity may reflect differences in causation and could have prognostic importance. (38 refs)

79-5860 Lymphomatoid Papulosis: A Recently Discovered Anatomical-Clinical Entity. (Ita) Eusebi, V. (Istituto di Anatomia e Istologia Patologia, Università di Bologna, Bologna, Italy); Bondi, A.; Bisighini, G.; Moroni, P. *Chronica Dermatol* 9(6): 651-660; 1978.

Three cases of lymphomatoid papulosis are reported. The differential diagnosis of this condition from diseases such as pityriasis lichenoides et varioliformis acuta, actinic reticuloid, mycosis

fungoides, and cutaneous lymphoma is considered, along with its histogenesis. (18 refs)

- 79-5861 Cutaneous Malignant Lymphoma in a Patient with Sarcoidosis. (Ita) Farris, A. (Divisione Dermatologica, Ospedali Civili di Genova, Genoa, Italy); Bacigalupo, A. *Chronica Dermatol* 9(6): 731-736; 1978.

A case of cutaneous malignant lymphoma developed in a 22-yr-old woman with sarcoidosis. The possible lymphomatous evolution of sarcoidosis is discussed. (30 refs)

- 79-5862 Pure Red Cell Aplasia and Lymphoma. (Eng) Carlsson, H. W. (Div. Hematology-Oncology, Scripps Clinic and Res. Foundation, 10666 N. Torrey Pines Road, La Jolla, CA 92037); Saab, G. A.; Tavassoli, M. *JAMA* 242(1): 67-68; 1979.

The case report of a 27-yr-old woman in whom pure red cell aplasia (PRCA) occurred several months after the diagnosis of poorly differentiated lymphocytic lymphoma is presented. PRCA was associated with lymphomatous infiltration of the bone marrow. Eighteen days after institution of therapy with doxorubicin hydrochloride-cyclophosphamide- vincristine-prednisone, clinical remission was achieved, and it was associated with the disappearance of malignant cells from the bone marrow and with the reappearance of RBC precursors. (6 refs)

- 79-5863 Primary Malignant Lymphoma of the CNS and Polyneuropathy in a Patient with Necrotizing Vasculitis Treated with Immunosuppression. (Eng) Jellinger, K. (Ludwig-Boltzmann-Institut für Klin. Neurobiologie, Krankenhaus Lanz, Wolkersbergenstrasse 1, A-1130 Vienna, Austria); Kothbauer, P.; Weiss, R.; Sunder-Plassmann, E. *J Neurol* 220(4): 259-268; 1979.

The development of peripheral neuropathy and a rapidly progressing cerebral disorder suggestive of a basal meningeal process was seen in a 58-yr-old woman who had undergone treatment with corticosteroids and azathioprine for generalized necrotizing vasculitis. Cerebrospinal fluid cytology suggested malignant lymphoma with meningeal involvement, and immunological studies showed an increase in null lymphocytes in the peripheral blood. Autopsy disclosed a primary malignant lymphoma of the CNS with the histologic appearance of a multilocal immunoblastoma showing almost ubiquitous meningeal involvement. Clinical and postmortem examinations failed to demonstrate any systemic extraneural lymphoproliferative disorder. There was peripheral polyneuropathy of the axonal type with denervation atrophy of the skeletal muscle, but without lymphomatous involvement of the neuromuscular system. The pathogenic background of peripheral polyneuropathy is unknown. (44 refs)

- 79-5864 Manifestation of a Highly Malignant Lymphoma in the Terminal Stage of Mycosis Fungoides. Enzyme Cytochemical and Immunocytological Investigations. (Ger) Buchner, S. (Dermatologische Klinik und Poliklinik, Universität Basel, Petersgraben 4, CH-4031 Basel, Switzerland); Rufli, T. *Dermatologica* 159(2): 125-131; 1979.

After a 24-yr history of mycosis fungoides, a 50-yr-old man rapidly developed a generalized highly malignant lymphoma. The diagnosis was confirmed by cytomorphological and enzyme cytochemical methods (demonstration of hydrolytic enzymes in cryostat sections, cutaneous smears, and cell suspensions extracted from skin lesions), as well as by immunocytological methods (differentiation of lymphocyte subpopulations). In the tumor stage of mycosis fungoides, a polymorphous infiltrate composed of lymphocytoid and monocytoid cells prevailed, but a proliferation of lymphoblastic cells was present in the terminal stage. These cells no longer showed the properties of mature lymphocytes, and they also differed in their enzyme-cytochemical pattern. (19 refs)

- 79-5865 Lymphatic Metastasis of Tumour; Persistent Transport of Cells. (Eng) Carr, J. (Dept. Physiology, Univ. Saskatchewan, Saskatoon, Saskatchewan, S7N 0W0, Canada); Carr, I.; Dreher, B.; Franks, C. R. *Experientia* 35(6): 825-827; 1979.

A model of lymphatic metastasis established by injecting Walker rat carcinoma cells into the footpad of outbred albino rats was used to study the output of tumor cells from the footpad. The presence of metastasis was established by histological examination of step paraffin sections of the ipsilateral popliteal lymph node. Injection of 20 million tumor cells of >90% viability into adult rats produced metastasis in >90% of the animals. The lymphatic efferent from the footpad was cannulated in a group of rats with advanced neoplasm. All 12 tumor bearing animals were cannulated successfully 7-9 days after transplantation. Tumor cells were seen in the lymph in all samples taken. All animals had metastasis in the popliteal lymph node. It was shown that the output of tumor cells via a single lymphatic efferent was continuous over periods up to 90 min and ranged from 10^2 to 10^5 cells/min. Broadly, the number of tumor cells leaving the footpad by a single lymphatic was directly related to the size of the primary tumor. (6 refs)

- 79-5866 Leukemia Occurring in Treated Hodgkin's Disease: Two Neoplasms or One? (Eng) Sheibani, K. (Div. Lab. Medicine, Cleveland Clinic, Cleveland, OH); Tubbs, R. R.; Savage, R. A.; Valenzuela, R.; Sebek, B. A.; Hewlett, J. S. *Cleve Clin Q* 46(2): 39-47; 1979.

A 46-yr-old man developed a second, morphologically distinct neoplasm approx 2 yr after the onset of nodular sclerosing Hodgkin's disease, Stage I. The patient had received 4,000 rads to the right and left supraclavicular lymph node areas at the time of diagnosis and, 8 mo later, he was started on MOPP (nitrogen mustard, vincristine, prednisone, procarbazine) chemotherapy. At the start of chemotherapy, a posterior iliac crest bone marrow (BM) biopsy specimen contained small foci of undifferentiated cells suggestive of acute monocytic leukemia. About 10 mo later, BM aspirate and a BM biopsy revealed complete replacement with primitive cells having pleomorphic folded nuclei suggestive of histiocytic lymphoma or monocytic leukemia. The patient died 1 mo later. At no time during the course of his illness were malignant cells identified in the peripheral blood. At autopsy, pleural nodules were found. The infiltrate in these nodules and in the BM consisted of large pleomorphic mononuclear cells with vesicular nuclei and prominent basophilic nucleoli. Binucleate and multinucleate variants were also found, but typical Reed-Sternberg cells (diagnostic of the original neoplasm) were not identified. The results of comparative studies of the two neoplasms showed cytochemical, cytologic, and immunologic differences. The reac-

tivity of cells from the two neoplasms toward sheep RBC (SRBC) and SRBC coated with antibody and complement was also different. It is suggested that the evolution of treated Hodgkin's disease may involve a change in the cytochemical and immunologic characteristics of the neoplasm, possibly reflecting a selective effect of treatment of varying cell types within the original neoplasm, and that the second neoplasm represented an overgrowth of one component of a single neoplasm rather than a new malignancy. (8 refs)

- 79-5867 Possible HLA Role in a Family with Hodgkin's Disease. (Eng) Nunez-Roldan, A. (Histocompatibility Lab., Dept. Biochemistry, Univ. Hosp., Seville, Spain); Martinez-Guibelalde, F.; Gomez-Garcia, P.; Gomez-Pereira, C.; Nunez-Ollero, G.; Torres-Gomez, A. *Tissue Antigens Histocompat Immunogenet* 13(5): 377-378; 1979.

Three siblings from a family of seven children were found to have Hodgkin's disease (mixed cellularity type) within 1 mo. Histocompatibility locus antigen (HLA) typing revealed that all three siblings had inherited the same haplotype from each parent; ie, A1-B5 from the mother and A26-B18 from the father. The coincidence of Hodgkin's disease in the only siblings who possessed the same HLA genotype suggests an association of the major histocompatibility complex genes and susceptibility to the disease within this family. The development of the disease in all three siblings within 1 mo suggests that a virus might also be involved. (4 refs)

- 79-5868 The Coexistence of Parathyroid Adenoma and Thyroid Carcinoma. (Eng) Calcaterra, T. C. (Div. Head and Neck Surgery, UCLA Sch. Medicine, Los Angeles, CA 90024); Paglia, D. *Laryngoscope* 89(7, part 1): 1166-1169; 1979.

The possible significance of the relationship between parathyroid adenoma and nonmedullary thyroid carcinoma was studied. Among a series of 144 patients with parathyroid adenoma, 11 had concurrent thyroid carcinoma. Although these two tumors are similar to other multiple endocrine tumor syndromes, they have no common embryonic cell origin. The most likely explanation for this apparent relationship is the specific oncogenic effect of hypercalcemia on the thyroid gland. (9 refs)

- 79-5869 Report of a Case of Recklinghausen's Disease Associated with a Pituitary Adenoma. (Ita) Barberis, M. (Istituto di Anatomia patologica, Ospedale Maggiore "Ca' Granda" di Milano-Niguarda, Milan, Italy); Gambacorta, M.; Versari, P.; Filizzolo, F. *Pathologica* 71(1012): 265-272; 1979.

A case of cutaneous and visceral von Recklinghausen's disease associated with an acidophilic pituitary adenoma is reported. (9 refs)

- 79-5870 Familial Endocrine Adenomatosis. (Ger) Muhlenstedt, D. (Institut für Humangenetik, Vesaliusweg 12/14, D-4400 Münster, W. Germany); Schneider, H. P.; Lenz, W. *Med Klin* 74(14): 520-523; 1979.

The combination of pituitary and thyroid gland adenomatosis oc-

curred in four family members of two generations. The finding of a dominant inheritance is discussed with special reference to multiple endocrine adenomatosis (Wermer's syndrome). The endocrine status of the patients, including the results of dynamic function tests, is presented. In cases of monoglandular adenomatosis, clinical attention should be directed not only to the anterior pituitary and thyroid glands, but also to the possible simultaneous occurrence of tumors of the parathyroid gland or the pancreas. (27 refs)

- 79-5871 Metastases in the Hypophysis. (Ger) Grabow, D. (Pathologisches Institut der Ernst-Moritz-Arndt-Universität, Friedrich-Loeffler-Strasse 23e, DDR-22 Griefswald, E. Germany); Schwesinger, G. *Zentralbl Neurochir* 40(1): 29-34; 1979.

Among 1,521 autopsies of patients with extracranial malignancies, 64 cases of metastases to the hypophysis were found. The primary cancer was breast carcinoma in 21.4% of the cases, malignant melanoma in 19.0%, and sympathoblastoma in 12.5%. Generalized metastases were found in 59/64 patients, indicating that hypophyseal involvement occurs during advanced disease stages. (15 refs)

- 79-5872 Coexisting Benign Mixed Tumor and Mucoepidermoid Carcinoma of the Parotid Gland. (Eng) Pontilena, N. (Dept. Otolaryngology, Columbia-Presbyterian Medical Center, New York, NY); Rankow, R. M. *Ann Otol Rhinol Laryngol* 88(3, part 1): 327-330; 1979.

Multiple unilateral parotid gland tumors are very rare. A review of the literature shows only seven cases of coexisting unilateral parotid tumors. The eighth case, a benign mixed tumor and a mucoepidermoid carcinoma of the right parotid gland, is described. The patient was a 45-yr-old woman who noticed a swelling in the right parotid region approx 10 yr prior to her admission. She denied pain in the mass, facial asymmetry, or any sudden increase in the size of the mass. Permanent sectioning of the parotid specimen revealed two discrete tumors. One tumor demonstrated one large and several smaller cystic spaces filled with a basophilic myxoid material and lined by one or two rows of cuboidal or low columnar cells. This was a benign mixed tumor. The second tumor was a low-grade mucoepidermoid carcinoma consisting of solid sheets of squamous epithelial cells and glandular structures lined by tall columnar cells and occasional goblet cells. These were separated by dense fibrous connective tissue. This the the first case of multiple unilateral parotid tumors to show such a tumor combination. (15 refs)

- 79-5873 Case Report. Turcot's Syndrome and Its Mode of Inheritance. (Eng) Itoh, H. (Dept. Surgery I, Kyushu Univ. Faculty Medicine, Maedashi 3-1-1, Fukuoka, Japan 812); Ohsato, K.; Yao, T.; Iida, M.; Watanabe, H. *Gut* 20(5): 414-419; 1979.

The occurrence of malignant cerebral neoplasms (grade 3 astrocytomas) in two sisters with Turcot's syndrome (TS) and colonic polyposis is reported. The parents of the patients were first cousins; neither had colonic polyps or neurological disorders. In two previously reported familial cases of TC, the disease occurred in both sexes but only among siblings. Neither colonic polyposis

nor brain tumors were found in the parents or other members of the families. In one of these two cases, the patient's parents were third cousins. It is concluded that the mode of inheritance of TC is autosomal recessive and that this disorder is genetically distinct from the ordinary form of familial polyposis coli. The absence of an association between the two disorders is supported by differences in the number, size, and distribution of colonic polyps. (17 refs)

- 79-5874 Widespread Carcinomatous Infiltration of the Meninges. (Ger) Steinhausl, H. (Neurologische Abteilung, Wagner-Jauregg-Krankenhaus, Wagner-Jauregg-Weg 15, A-4020 Linz, Austria). *Wien Med Wochenschr* 129(12): 341-343; 1979.

The case report of a 38-yr-old woman with meningeal carcinomatosis is presented, and the clinical picture of this condition is discussed. Examination of the cerebrospinal fluid is the most useful procedure for diagnosing of meningeal carcinomatosis. The clinical picture is very similar to that of meningitis tuberculosa. (5 refs)

- 79-5875 Recurrent Orbital and Metastatic Melanoma in a Patient Undergoing Previous Glaucoma Surgery. (Eng) Singer, P. R. (Dept. Ophthalmology, Washington Univ. Sch. Medicine, 660 S. Euclid Ave., St. Louis, MO 63110); Krupin, T.; Smith, M. E.; Becker, B. *Am J Ophthalmol* 87(6): 766-768; 1979.

A 61-yr-old woman with unilateral acute angle-closure glaucoma underwent a Scheie filtering operation. After a 2-wk interval, a large choroidal and ciliary body melanoma was found in the glaucomatous eye. There was no evidence of metastatic disease, and the eye was enucleated. Histopathologic sections did not show extrascleral extension. After 2.5 yr, the patient developed local orbital recurrence of the melanoma and fatal metastatic disease. A possible causal relationship between the filtering surgery and the local and systemic recurrence of the tumor is hypothesized. (7 refs)

- 79-5876 Two Cases of Intraepidermal Squamous Cell Carcinoma (Bowen's Tumor). (Rum) Jalobceastii, L. (No affiliation given.); Buiuc, S.; Beschea, G. *Rev Chir [Oftalmol]* 23(1): 77-79; 1979.

Two clinical cases of Bowen's tumor (intraepidermal squamous cell carcinoma) developed on the limbus and extended to the cornea of two men aged 37 and 64 yr. Examination of the lesions revealed thickening of the epithelium, mitosis in all epithelial layers, dyskeratosis, and an intact basement membrane. (10 refs)

- 79-5877 Malignant Melanoma of the Choroid in Melanosis Oculi. (Ger) Hubel, K. (Univ.-Augenlinik, Auenbruggerplatz 4, A-8036 Graz, Austria); Hanselmayer, H. *Klin Monatsbl Augenheilkd* 174(3): 404-407; 1979.

A malignant melanoma of the choroid developed in a 33-yr-old woman with melanosis oculi. The incidence of malignant melanoma is much higher in patients with melanosis oculi than in

normal subjects. Regular (every 1-2 yr) microscopic examinations should be made of such patients in order to detect the development of a melanoma at an early stage. (13 refs)

- 79-5878 The Small Congenital Nevocytic Nevus and Malignant Melanoma (Letter to Editor). (Eng) Kirschenbaum, M. B. (6450 N. California Ave., Chicago, IL 60645). *JAMA* 242(1): 26; 1979.

Although malignant melanoma has been reported to occur in the large "bathing trunk nevus" in up to 20% of patients, there is little evidence that malignant transformation occurs in small, congenital, nevocytic nevi. (no refs)

- 79-5879 Correlation Between Differentiation and Malignancy in Human Malignant Melanocytes In Vivo and In Vitro. (Fre) Foa, C. (Unité 119 de l'Inserm, 27 Boulevard Leirou, F 13009 Marseille, France). *Bull Cancer (Paris)* 66(3): 287-292; 1979.

Cell lines established from human primary malignant melanomas were studied in order to correlate their ultrastructural and biochemical characteristics and their malignant potential. Variability in the size of the cell and nucleus, the type and number of melanosomes, the presence of concentric bodies and vacuoles, etc, was accompanied by variability in the location of dopaoxidase (Golgi bodies, endoplasmic reticulum, small vesicles), level of 5-S-cysteinyl-dopa, and chromosome pattern. The malignant potential of the cultured cell lines was tested by heterotransplantation into hamster cheek pouches and nude mice. Both the in vivo and in vitro studies showed that a relationship between melanization and malignant potential cannot be established. Highly pigmented human melanoma cell lines were more likely to give rise to tumors in experimental animals; however, achromic cell lines were also heterotransplantable, and one highly pigmented cell line was not heterotransplantable. (80 refs)

- 79-5880 Histological Classification of Primary Melanoma in Relation to Therapeutic Procedures and Prognosis. (Yug) Jakasa, V. (Sredisnji institut za tumore i slicne bolesti, Zagreb, Yugoslavia); Popovic, S.; Kosanovic, S.; Maricic, Z.; Nola, P. *Lijec Vjesn* 101(2): 70-72; 1979.

Excluding rare melanomas originating in a blue nevus, primary cutaneous melanomas can be divided into three histogenetic types: (1) invasive melanoma with superficial spreading, (2) nodular melanoma, and (3) invasive melanoma originating from the melanotic freckle of Hutchinson. The depth of invasion can be divided into five stages. Among 48 patients with invasive primary melanoma, there were 30 melanomas with superficial spreading, 12 nodular melanomas, and 6 unclassified types. In 29/33 patients in whom cytological analyses were made, the findings corresponded to the pathohistological ones; in 3 patients, the findings were suspect, and in 1 they were falsely negative. Most (11) patients had polygonal melanocytes; fusiform melanocytes were found in 5 patients, and mixed-type melanocytes in 9. In 4 patients, the cells were polymorphic. (14 refs)

- 79-5881 Familial Hereditary Malignant Melanoma. (Ger) Landthaler, M. (Dermatologische Universitätsklinik,

Frauenlobstrasse 9, D-8000 Munich 2, W. Germany); Braun-Falco, O. *Med Klin* 74(10): 353-357; 1979.

The frequency of familial hereditary malignant melanoma (MM) is estimated to be 1%-7% of all MM's. It occurs by an autosomal-dominant mode of inheritance with reduced penetrance or a polygenetic mode of inheritance. Patients with numerous inherited atypical nevi, the so called BK moles, are reported to have a high incidence of MM. Hereditary MM's begin early in life, are often multiple, and are associated with other malignant tumors in afflicted families. Men are affected as often as women. Five families with hereditary MM are described, and the literature is reviewed. (49 refs)

- 79-5882 Multiple Juvenile Melanoma in a Large Melanotic Birthmark. (Ita) Muscianese, V. (IV Divisione, Sezione Pediatrica, Istituto Dermatologico dell'Immacolata, Rome, Italy); Paradisi, M.; Voglino, A.; Carbone, F. *Chronica Dermatol* 9(6): 643-650; 1978.

A case of multiple juvenile melanoma in a large melanotic birthmark on the right cheek of a 16-mo-old child is reported. A few days after birth, a small pigmented nevus appeared on the cheek. The lesion was initially smooth and reddish grey, but with time it developed into a grey-black, slightly wartlike lesion that covered the entire parotid region. At 11 mo of age, small rose-colored papules appeared in the area; over a 4- to 5-mo period, they reached the size of a lentil. On presentation, the slightly raised lesion had regular margins and about 30 reddish grey papules (2- to 5-mm in diameter) distributed over its surface. All the laboratory tests were negative or within normal limits. Histological examination revealed hyperplasia of the melanocytes. In the dermis, numerous nevus cells were seen, and within the lesion, nodules that contained little or no pigment were observed. A few lymphocytes were seen along the margins of the nodules. The lesion had the characteristics of Spitz nevus. (23 refs)

- 79-5883 Idiopathic Retroperitoneal Fibrosis in Children. (Eng) Chan, S. L. (Urology Clinic, Univ. British Columbia, Vancouver, British Columbia); Johnson, H. W.; McLoughlin, M. G. *J Urol* 122(1): 103-104; 1979.

A case of idiopathic retroperitoneal fibrosis (IRF) in an 11-yr-old boy is presented. A review of seven previous cases in children revealed that there was no characteristic presentation in this disease process and that the diagnosis usually is suspected on an excretory urogram. In adults, IRF has been associated with occult malignancy, which has been implicated as a causative agent in this retroperitoneal process. (10 refs)

- 79-5884 Cutaneous Lupus Erythematosus Associated With Melanoma and BCG Vaccine Therapy. (Eng) Herstoff, J. K. (Div. Dermatology, Dept. Medicine, Roger Williams General Hosp., Providence, RI); Bogaars, H. A. *Arch Dermatol* 115(7): 856-859; 1979.

Two cases of the development of cutaneous lupus erythematosus (LE) after the appearance of a melanoma are reported. A 53-yr-old man was treated with intradermal BCG vaccine and ibuprofen therapy for widespread Stage II metastatic melanoma. LE erupted shortly after the commencement of BCG therapy, but did not sub-

side when the drug therapy was discontinued. In a 67-yr-old man with more localized Stage II melanoma, LE subsided after the melanoma was excised. Neither patient had symptoms of systemic LE and, in general, laboratory data did not suggest visceral disease. However, results of direct immunofluorescence assay demonstrated immunoglobulin deposits and complement in the uninvolved, sun-exposed skin of both patients. Neither patient manifested renal involvement. The first patient had positive serum antinuclear antibody (ANA) results in low titer, and the second did not have ANA in his serum. (14 refs)

- 79-5885 Epitheloid Sarcoma: A Case Report. (Eng) Button, M. (4511 S.E. Hawthorne Blvd., Portland, OR 97215). *J Hand Surgery* 4(4): 368-371; 1979.

A case of epitheloid sarcoma of the pulp of the thumb developed following repeated penetrating injuries. The patient first sustained a penetrating injury to the pulp of the thumb from a clean, broken pipette. The wound healed and became asymptomatic, but a similar injury to the same area occurred 12 yr later and resulted in a slowly enlarging mass; the mass and glass fragments were removed, but recurrence and diagnosis of epitheloid sarcoma upon review of the slides of the initial specimen necessitated amputation of the thumb. (14 refs)

- 79-5886 Ultrastructural Studies on Osteoclastoma. (Eng) Panicker, K. N. (Tata Memorial Centre, Bombay 400 012, India); Potdar, G. G.; Sirsat, S. M. *Indian J Exp Biol* 17(1): 9-14; 1979.

Five biopsy specimens of osteoclastoma of the bone were studied light and electron microscopically. The specimens were comprised of polygonal stromal cells, fibroblasts, lipid-laden foam cells, and multinucleated giant cells. The giant cells showed ultrastructural evidence of phagocytic activity. The other cell types were morphologically more differentiated than the giant cells. Ultrastructural study confirmed the possible origin of this tumor from undifferentiated mesenchymal cells through an intermediate advanced type of cell, the osteoclast. The term "osteoclastoma" is more suitable than "giant cell tumor" and it avoids confusion regarding the origin of this tumor entity. (10 refs)

- 79-5887 Spindle Cell Carcinoma Arising in Chronic Osteomyelitis. A Case Report and Re-assessment of the Literature. (Eng) Hill, J. A. (Dept. Orthopaedic Surgery, Northwestern Univ. Medical Sch., 303 East Chicago Avenue, Chicago, IL 60611); Battifora, H. A.; Milgram, J. W. *Bull Hosp Joint Dis* 39(2): 187-195; 1979.

The occurrence of spindle cell carcinoma is reported in a 65-yr-old woman who had chronic osteomyelitis of the left tibia since the age 12 yr. Biopsy of the sinus tract led to a pathological diagnosis of sarcoma, type unknown, with areas of poorly differentiated epidermoid carcinoma. The patient subsequently underwent left above-knee amputation; the predominant pattern in the surgical specimen was short, criss-crossing fascicles of pleomorphic spindle cells with occasional atypical multinucleated giant cells. Although there were many light microscopic features suggestive of a sarcoma, in particular angiosarcoma, the ultrastructural features were suggestive of epithelial histogenesis. A diagnosis of spindle cell carcinoma was made. The patient did well after surgery with

no evidence of metastases or local recurrence 1 yr later. Electron microscopy may be useful in differentiating true fibrosarcoma from spindle cell carcinoma arising in chronic osteomyelitis. (17 refs)

- 79-5888 Cancer of the Larynx in Women. (Fre) Perrin, C. (Service O.R.L., C.H.U. de Nancy-Brabois, 54500 Vandoeuvre-les-Nancy, France); Long, F. X. *J Fr Otorhinolaryngol* 28(5): 291-294, 297; 1979.

Among a series of 160 patients with cancer of the larynx, eight were women aged 47-84 yr. These women were heavy smokers, at least 20 g/day, and some also used alcohol heavily. Three patients had a family history of ear, nose, and throat cancer. The duration of symptoms (primarily dysphagia) prior to diagnosis ranged from 1 mo (2 patients) to 3 yr (1 patient). Seven women had a differentiated epidermoid carcinoma, and one had an atypical carcinoma. In one patient, the lesion was limited to one ventricular band; however, leukoplakia was observed on the other band. The lesions were extensive in three patients, involving both the hyper- and hypopharynx. In three patients, the cancers involved one side of the larynx and bordered on the adjacent piriform sinus; in one, the cancer involved the entire endolarynx. (no refs)

- 79-5889 Characteristic Features of Laryngeal Carcinoma in Women. (Rus) Iudov, N. N. (Dept. Otorhinolaryngology, Medical Inst. Altai Krai, Altai Krai, USSR); Zavarzin, A. A.; Simonova, I. A. *Vestn Otorinolaringol* (4): 53-55; 1979.

Clinical findings in a group of 100 female laryngeal cancer patients (aged 23 to 86 yr; median age group 50-59 yr) and 300 male patients were compared. It was found that 62% of the women smoked and 39% consumed alcohol, compared with 92% and 80%, respectively, of the men; precancerous lesions of the larynx were diagnosed in 17% of the women and 18% of the men. Regional lymph node metastases were detected in 10% of the women and 18.7% of the men. The women had a better 5-yr survival rate. (11 refs)

- 79-5890 Study of Amylase-producing Lung Cancer. (Jpn) Fukuda, H. (Dept. Thoracic Surgery, Chest Disease Res. Inst., Kyoto Univ., Kyoto, Japan); Ito, M. *Bull Chest Dis Res Inst Kyoto Univ* 12(1/2): 36-45; 1979.

Amylase activity in the resected tumor tissue of lung cancer patients was investigated biochemically, microscopically, histologically, and immunohistochemically. The subjects included 8 patients with adenocarcinoma, 7 with squamous cell carcinoma, 3 with undifferentiated carcinoma, and 1 with cylindroma. Controls were patients who underwent lung, bronchial, liver, or pancreatic resection. Compared with controls, only 2/8 adenocarcinoma specimens showed high amylase activity. Electron microscopic examination revealed small zymogen granulelike vacuoles and free ribosomes in the amylase-producing tumor cells. These cells showed a specific fluorescence for amylase with an alcian blue stain. The serous cells of the bronchial gland of control adults and fetuses also showed a specific fluorescence for amylase, as did certain peripheral cells of fetal lung tissue. The origin of the amylase-producing cells in patients with adenocarcinoma of the

lung may be the serous cells of the bronchial gland and certain peripheral lung cells. (20 refs)

- 79-5891 Histologic and Ultrastructural Features of the Clara Cell Adenoma of the Mouse Lung. (Eng) Kauffman, S. L. (Dept. Pathology, State Univ. New York, Brooklyn, NY); Alexander, L.; Sass, L. *Lab Invest* 40(6): 708-716; 1979.

Lung adenomas were induced by the transplacental exposure of Swiss Bagg-Webster mice to ethylnitrosourea (0.75 mM/kg ip) on the 16th day of gestation. The lungs of postnatal animals 1-3 mo of age were examined grossly, and step sections were made of the right lower lobe for light microscopy. Additional tumors were fixed in Palade's solution and prepared for light and electron microscopy. Tumors were classified on the basis of their predominant histologic pattern as alveolar or bronchiolar, and the tumor cell type was identified by electron microscopy. Of the 149 adenomas found in the right lower lobes, 86 were bronchiolar and 61 were alveolar. The bronchiolar papillary tumors consisted of Clara cells, the nonciliated epithelial cell of the terminal bronchioles, whereas the alveolar tumors consisted of type II alveolar cells. The Clara cell has not previously been recognized as a progenitor cell of murine lung adenomas; however, these cells form tumors that are clearly distinguishable from type II alveolar cell adenomas. Because the Clara cell tumor may have a malignant potential not shared by the type II cell adenoma, it is important to classify mouse lung adenomas according to their cell of origin, particularly when evaluating the progression of chemically induced tumors. (59 refs)

- 79-5892 Pulmonary Siderosis and Bronchopulmonary Cancer. A Case Report. (Fre) Caillard, J. F. (Institut de médecine du travail, C.H.U. de Caen, Caen, France); Lemenager, J.; Wyplotz, J.; Mandard, J. C.; Chasles, J.; Benard, Y.; Le Bouffant, L. *Arch Mal Prof* 40(1/2): 52-53; 1979.

An aggregated form of pulmonary siderosis and a 5- to 6-cm adenocarcinoma of the right upper lobe were diagnosed in a 51-yr-old metal polisher who had been exposed to iron and iron oxide dust for >15 yr. An inflammatory pseudotumor was found in the lingula of the left upper lobe. (no refs)

- 79-5893 Pleomorphic Pulmonary Hamartoma. An Apparently Unique Variant of Pulmonary Hamartoma. (Eng) Gisser, S. D. (Dept. Pathology, Cooper Medical Center, Camden, NJ); Young, I. *Hum Pathol* 10(4): 393-403; 1979.

A well-circumscribed, nonencapsulated, noninvasive tumor discovered accidentally in the lung of a 41-yr-old black man is described. The patient had been a moderate smoker for 20 yr. The tumor was associated with anomalous lung segmentation and the bronchial and blood supply to the lung. The tumor appeared to be undifferentiated, and light microscopy alone led to various erroneous diagnoses, including neurilemoma, leiomyoma, ganglioneuroblastoma, and teratoma. Electron microscopy showed a highly complex but incompletely organized array of cellular elements similar to those seen in mature and developing pulmonary tissue. These elements included well-differentiated epithelial elements, some ciliated and some mucin-producing, as well as undifferentiated mesenchyme. The mass represented a unique, probably hamartomatous, tumor. (15 refs)

- 79-5894 Scleroderma with Carcinoma of the Esophagus. Case Report. (Eng) Whitaker, J. A. (Dept. Gastroenterology, Wesley Medical Center, 550 N. Hillside, Wichita, KS 67214); Bishop, R. *Am J Gastroenterol* 71(5): 496-500; 1979.

An esophageal carcinoma developed in a 48-yr-old man with scleroderma. An antiesophageal regimen was instituted. The patient was readmitted 23 mo later with dysphagia, wt loss, and substernal chest pains. A barium swallow revealed a fungating lesion that nearly obstructed the esophagus. Biopsy of a nodular mass proved to be a moderately differentiated squamous cell carcinoma. Despite the fact that the esophagus of scleroderma patients is chronically irritated because of acid reflux, the development of esophageal carcinoma in these patients probably is a rare event. (26 refs)

- 79-5895 Zenker's Diverticulum. Carcinoma of the Esophagus? (Eng) Rojas, F. A. (Dept. Otolaryngology, Henry Ford Hosp., 2799 W. Grand Boulevard, Detroit, MI 48202); Szymanowski, R.; Fujita, S. *J Otolaryngol* 8(3): 266-270; 1979.

The case of a 67-yr-old man who developed a squamous cell carcinoma in a Zenker's diverticulum is reported. The patient presented with dysphagia of several mo duration. There was an associated regurgitation of food that had become more severe the month before admission. An esophagram revealed a Zenker's diverticulum, but no tumor or mucosal abnormality was detected by hypopharyngoscopy and esophagoscopy prior to surgery. The diverticulum was excised and found to be infiltrated by squamous cell carcinoma. Radiotherapy consisting of 6,000 R over a 6 wk period was administered. Five months after the first admission, the patient was again suffering from progressive dysphagia. Laryngoscopy and esophagoscopy showed a friable mass (6 x 5 cm) in the hypopharynx and upper esophagus, and histological examination revealed well-differentiated epidermoid carcinoma. A laryngopharyngectomy with partial esophagectomy was performed. (13 refs)

- 79-5896 Gastric Polyps. (Ita) Ciciliot, V. (Ente Ospedaliero San Paolo, Ospedale Generale Provinciale, Savona, Italy); Roggero, F.; Grandis, C.; Oliveri, M. *Minerva Dietol Gastroenterol* 25(2): 209-222; 1979.

The occurrence, description, and classification of gastric polyps and tumors are reviewed, with particular reference to 24 cases encountered during 2,450 instances of gastric surgery. Most (60%-70%) gastric polyps are of epithelial origin. They are of four types: submucosal masses (benign), types I and III sessile polyps (each, benign and malignant), and pedunculated polyps (benign and malignant). Leiomyomas are the most frequent nonepithelial gastric tumors; however, their incidence is quite variable in different literature reports. Leiomyoblastomas are usually benign gastric tumors of muscular origin, and they show microfibrils microscopically. Lipomas represent 0.06%-7.2% of all benign gastric tumors; they are usually localized in the antrum, where they arise from connective tissue. Three types of nervous system tumors occur in the stomach. Neurilemmomas, which represent about 70% of these tumors, occur most frequently in the distal portion of the stomach, arising from myelinated fibers. Neurofibromas represent about 25% of nervous system gastric tumors, and they arise generally throughout the stomach. The remaining 5% of nervous system gastric tumors are neuroblastomas and paragangliomas,

which arise in the sympathetic nervous system. Gastric tumors containing pancreatic elements, gastric vascular tumors, and gastric fibromas also occur. The 24 patients (14 women and 10 men aged 45-88 yr) had histologic diagnoses of adenomatous polyps (12 cases), polyps with malignant change (5), leiomyomas (2), a pancreatic-type tumor, a fibromyoma, a leiomyoblastoma, a lipoma, and a granuloma. Clinical data for these patients are tabulated. (58 refs)

- 79-5897 Peptic Esophagitis and Carcinoma of the Lower Third of the Esophagus: Report of 7 Cases. (Fre) Hureau, J. (Clinique Therapeutique Chirurgicale, Hopital de Vaugirard, 389, rue de Vaugirard, 75-Paris, France); Bourdais, J. P.; Delavierre, P.; Vayre, P. *J Chir (Paris)* 116(3): 167-174; 1979.

Carcinoma of the lower third of the esophagus was diagnosed in 7 patients (4 men and 3 women, aged 41-82 yr) with chronic peptic esophagitis. The tumor was identified as adenocarcinoma in 5 cases, as epidermoid carcinoma in 1, and as epidermoid carcinoma in situ in another. The duration of the esophagitis before the diagnosis of the carcinoma could be established in 5 cases, ranging from 6 to 32 yr in 4, and probably 3-5 mo in 1. The findings indicate that peptic esophagitis of the lower third of the esophagus can be precancerous and that chronic cases require regular follow-up. (35 refs)

- 79-5898 Esophagogastroplasty in Upper Esophageal Lesions: 4 Cases. (Ita) Olivero, S. (Istituto di Chirurgia d'Urgenza, Università degli Studi di Torino, Turin, Italy); Ibba, F.; Viglione, G. C.; Sanfelici, G.; Foco, A.; Garbarini, A.; Bertoldo, U.; Serenitha, U.; Bronsino, E.; Buniato, E.; Vottero, G. *Minerva Chir* 34(7): 511-524; 1979.

An esophagogastroplasty was performed in four patients, three with a neoplastic lesion of the upper esophagus and one with mediastinal compression due to sclerosing mediastinitis. The technique is described in detail, and indications for the surgery are given. (15 refs)

- 79-5899 Identical Malignant Tumors in Siblings and Twins. (Hun) Cserhati, G. (Sebeszeti Osztaly, Varosi Korhaz, Mosonmagyaróvár, Hungary); Szilagyi, J. *Orv Hetil* 120(20): 1195-1196; 1979.

Rectal adenocarcinomas were diagnosed in 69-yr-old twin brothers within 22 days. Both patients had blood type AB and were Rh-positive. Inoperable malignant gastric tumors of the same localization were found in two brothers aged 60 and 63 yr, respectively. Both had blood type A and were Rh-positive. The tumors were not classified histologically. The findings suggest that these tumors had a genetic origin. (4 refs)

- 79-5900 Successful Surgery for Malignant Neurinoma Originating in the Stomach. (Hun) Zolnay, B. (Sebeszeti Osztaly, Semmelweis Korhaz, Miskolc, Hungary); Radvanyi, G.; Kostyal, A. *Orv Hetil* 120(24): 1449-1451; 1979.

A malignant neurinoma originating in the muscular layer of the gastric mucosa was diagnosed in a 66-yr-old man 12 yr after

Billroth II resection for duodenal ulcer and pyloric stenosis. The subserous tumor contained necrotic Schwann's cells. (20 refs)

- 79-5901 Leiomyosarcoma of the Duodenum. Case Report and Literature Review. (Spa) Costa Baptista, J. C. (Dept. de Cir., Fac. de Med., Hosp. de Clin., Marilia, Spain); Gerlach, S. M.; Gomes de Oliveira, G.; Tsuji, H.; Ribeiro de Melo, N.; Nakadaira, A. *AMB* 25(1): 28-30; 1979.

A rare case of leiomyosarcoma of the duodenum in a 59-yr-old man is presented. The patient was admitted with intense pain in the right iliac fossa and a 6 mo history of wt loss. He had undergone gastrectomy for duodenal ulcer 16 yr previously. Ten years previously, he had been hospitalized for interorrhagia, and a tumor 5 cm in diameter was observed in the right abdomen. Two years before diagnosis of the leiomyosarcoma, the tumor had increased to 10 cm in diameter and it was tender. The etiology, incidence, pathology, and diagnosis of duodenal leiomyosarcomas are discussed. (27 refs)

- 79-5902 In-Vitro Evidence for Adenoma-Carcinoma Sequence in Large Bowel (Letter to Editor). (Eng) Danes, B. S. (Lab. Cell Biology, Dept. Medicine, Cornell Univ. Medical Coll., New York, NY 10021). *Lancet* 2(8132): 44-45; 1979.

In vitro evidence for a progression from normal tissue to adenoma to carcinoma in the large bowel was obtained using cell lines established from the skin of 112 patients with adenomatosis of the colon and rectum (ACR) and 74 age- and sex-matched controls. Transformed cell populations growing in suspension arose in single monolayer sublines derived from five biopsies from four ACR patients. The changes indicative of transformation included altered morphology, ability to grow as single cells or clusters in suspension and on a surface, and a seemingly unlimited life-span in culture. The occurrence of transformed cell populations in some ACR sublines and not in those from controls supports the hypothesis that cells with genomes having certain mutations, such as the polyposis gene, are more susceptible than those without such mutations to changes in biological properties in vitro. The cellular changes noted in this study could be considered as just one in a series of changes that precede cancer. (3 refs)

- 79-5903 Anatomic, Pathologic, and Clinical Aspects of a Case of Carcinoid of the Ileum. (Ita) Sgro, M. (Divisione di Chirurgia Generale, Ospedale di Circolo, Busto Arsizio, Italy). *Minerva Chir* 34(7): 543-548; 1979.

The anatomopathological and clinical aspects of a case of carcinoid of the ileum that occurred in a 65-yr-old patient are presented. Attention is called to new histogenetic theories and classification criteria in the light of recent immunohistochemical, ultrastructural, and biochemical research. (27 refs)

- 79-5904 Leiomyosarcoma of the Jejunum with Lymphatic Dissemination. Report of a Case. (Por) Oliveira Almeida, H. (Dep. de Patol, Fac. de Med. do Triangulo Mineiro, Uberaba, Brazil); de Andrade, J. I.; Maluf, W.; Naves Junqueira, J. F. *AMB* 25(1): 18-20; 1979.

A rare case of well-differentiated leiomyosarcoma of the jejunum with lymph node metastases occurred in a 51-yr-old man. The differential diagnosis of this tumor from a benign leiomyosarcoma is very difficult. The histological data suggestive of malignancy in this case were moderate hypercellularity and irregular distribution of mitoses. (20 refs)

- 79-5905 Multiple Carcinoids of the Small Intestine. (Ger) Ernst, P. (Chirurgische Klinik, Städtisches Krankenhaus Berlin-Pankow, Galenus-strasse 60, 110 Berlin, W. Germany); Koch, P.; Bailleu, E. *Z Aerztl Fortbild (Jena)* 73(9): 448-450; 1979.

The difficulty of preoperative diagnosis of a carcinoid in the small intestine is illustrated by a case report of multiple carcinoids in a 75-yr-old woman who presented with diffuse peritonitis. This patient had suffered from spastic diarrhea and occasional constipation for several years, and she had recently undergone surgery for subileus. (16 refs)

- 79-5906 Malignant Transformation of Adenoma of Large Intestine. (Jpn) Yamagiwa, H. (Dept. Clinical Pathology, Mie Univ. Sch. Medicine, Tsu, Japan); Ishihara, A. *Jpn J Cancer Clin* 25(7): 664-668; 1979.

A histological examination was made of 623 resected tumors from 600 patients with carcinoma of the large intestine (LIC: 54 early stage) and of 635 adenomas that were surgical, endoscopic, or autopsy specimens to determine the relationship between the adenomas found in large bowel polyps and LIC. Adenomas were found in 62/623 LIC's, and malignant transformation was seen in 62/697 adenomas found in areas of the malignant tumors. Adenomas >1 cm diameter, found most often in the rectum and sigmoid flexure, had a greater degree of atypia than those with a diameter of <1 cm. Malignant transformation was seen in 5.2% of the tubular adenomas, 78.9% of the tubulovillous adenomas, and 65% of the villous adenomas. Adenomas up to 1 cm in diameter showed very few malignant cells (approx 1%), and adenomas >1 cm showed increasing numbers of malignant cells. In contrast, villous adenomas, which occurred frequently in the rectum and sigmoid flexure, showed no signs of transformation up to a diameter of 4 cm. The incidence of remnants of adenomas was related to the depth of tumor infiltration; it was 93.1%, 64%, 15.3%, and 1.7% with mucosal, submucosal, muscular, and serosal invasion, respectively. (17 refs)

- 79-5907 Malignant Lymphoma in Chronic Ulcerative Colitis. (Yug) Branica, H. (Odjel za patologiju i citologiju, Opca bolnica, Split, Yugoslavia); Bakotin, J.; Rubic, I. *Lijec Vjesn* 101(2): 88-90; 1979.

The case report of a 36-yr-old man who had chronic ulcerative colitis for 6 yr is given. Total proctocolectomy was performed because of repeated attacks of abdominal pain and diarrhea. The histopathologic report was chronic ulcerative colitis and non-Hodgkin's-type malignant lymphoma. The clinicopathologic aspects of this complication of ulcerative colitis are discussed, with special emphasis on the problem of correct diagnosis. (15 refs)

- 79-5908 Extramedullary Plasmacytoma of the Gastrointestinal Tract in a Renal Transplant Recipient. (Eng) Hara, H.

(Dept. Pathology, Kochi Medical Sch., Nankoku City, Kochi Prefecture 781-51, Japan); Yamane, T.; Yamashita, K. *Acta Pathol Jpn* 29(4): 661-668; 1979.

An extramedullary plasmacytoma (PC) of the gastrointestinal tract that developed in a 23-yr-old male renal transplant recipient was examined by an immunoglobulin (Ig)-enzyme bridge technique. Formalin-fixed, paraffin-embedded tissue sections were stained successively with specific rabbit anti-human IgG, IgA, and IgM and κ light chain antisera, goat anti-rabbit IgG antisera, and rabbit anti-horseradish peroxidase antisera. Most of the plasma cells in the gastric mucosa contained a single type of heavy-chain IgA and κ -type light chain, whereas plasma cells in the kidneys and liver were well-stained with various types of Ig. Pathological investigations revealed multiple similar tumors in the ileum, cecum, and ascending colon, suggestive of a multicentric origin. The patient had been treated with immunosuppressive agents after the renal transplant, and he appeared to be in an immune-deficient state. The development of the plasma PC might be an indirect complication of the renal transplantation or it might be related to the immune-deficient state. (16 refs)

79-5909 Rectal Polyp: A Preliminary Stage of Rectal Carcinoma? (Ger) Wayand, W. (I. Chirurgische Universitätsklinik, Alser Strasse 4, A-1097 Vienna, Austria); Roka, R. *Acta Chir Austriaca* 10(5): 113-115; 1979.

Seventy-three rectal polyps from 67 patients with solitary polyps of the rectum (Group 1) and 93 rectal polyps from 74 patients with rectal carcinoma (Group 2) were investigated for signs of malignant transformation. The incidence of atypia, increased number of mitoses, and so-called carcinoma in situ was 5/73 in Group 1 and 14/97 in Group 2. Invasion was seen in Group 1 (3/73 polyps) and in Group 2 (6/97 polyps). Most Group 1 patients were 55-64 yr old, and most Group 2 patients were 65-74 yr old. Eight polyps from Group 1 and 20 from Group 2 were investigated for type of dedifferentiation. In Group 1, 2 tubulovillous, 4 villous, and 2 tubulovillous polyps were found. In Group 2, 6 tubulovillous, 7 villous, and 7 tubulovillous polyps were found. The difference in the age distribution between the two groups suggests that rectal polyps evolve into carcinoma. (10 refs)

79-5910 Familial Urinary Bladder Cancer. (Eng) Purtilo, D. T. (Dept. Pathology, 55 Lake Avenue North, Univ. Massachusetts Medical Sch., Worcester, MA 01605); McCarthy, B.; Yang, J. P.; Friedell, G. H. *Semin Oncol* 6(2): 254-256; 1979.

The clinical and pathological features of 13 cases of bladder transitional cell carcinoma (TCC) in 6 unrelated families in the Worcester, Massachusetts, area illustrate the contention that genetic factors may play an important role in the etiology of bladder TCC. The affected individuals were two male siblings (aged 62 and 55 yr respectively at time of onset) in family 1, two male siblings (aged 59 and 56 yr) in family 2, brother and sister (aged 91 and 89 yr) in family 3, two male siblings (aged 39 and 52 yr) and family 4, two brothers and a daughter of the first brother (aged 33, 28, and 19 yr) in family 5, and a father and son (aged 73 and 62) in family 6. Occupational and smoking habit risks were prevalent in all these patients except those in family 3, the 52-yr-old patient in family 4, and the 19-yr-old patient in family 5. These cases of TCC displayed the major features of familial cancer: 1) affected individuals were younger than the usual non-familial cases; 2) multiple TCC with frequent recurrences and multiple genitourinary car-

cinomas occurred in families 3 and 4; 3) there was general concordance in types of cancer; and 4) there was concordance of age at time of appearance of TCC in siblings. The pattern of inheritance in families 5 and 6 suggests a Mendelian autosomal dominant trait. The possibility that an inherited predisposition to bladder TCC or a heightened susceptibility to environmental carcinogens operates in familial cases of bladder TCC is discussed. (18 refs)

79-5911 Nonpapillary Carcinoma In Situ of the Urinary Bladder. A Histopathologic Study and Mapping of the Urothelial Lesions. (Eng) Iwasaki, H. (Dept. Pathology, Fukuoka Univ. Sch. Medicine, 34 Nanakuma, Nishi-ku, Fukuoka 814, Japan); Enjoji, M.; Kano, M. *Acta Pathol Jpn* 29(4): 623-633; 1979.

Three cases of primary carcinoma in situ (CIS) of the bladder diagnosed by urinary cytology and multiple biopsies were studied in detail. In two cases, epithelial lesions were mapped completely to study the distribution of abnormal epithelium and to demonstrate the presence or absence of microscopic invasion. The patients, all men aged 53-66, had no histories of exposure to carcinogens; however, all three were smokers. Atypical hyperplasia and CIS with foci of microscopic invasion affected the bladder mucosa and extended continuously to the distal ureters and the prostatic urethra. A multicentric distribution of abnormal epithelium was definite in one patient, and the bladder mucosa was denuded extensively in another. Metastasis to one of the regional lymph nodes was noted in the third patient. Pagetoid cells that possessed abundant clear cytoplasm were found in two of the patients. They were found most frequently in the Brunn's nests and in the developing margin of the CIS. Their origin is obscure. They may represent transformed tumor cells showing differentiation toward the surface umbrella cells or they may be derived from Brunn's nests, where the cells may gain potential to differentiate to glandular epithelium. The finding in one patient of CIS in small isolated foci and in a single large area separated by nonneoplastic mucosa and often intermingled with atypical epithelium supports the multicentric origin of CIS and indicates its intimate relationship to atypical epithelium. (18 refs)

79-5912 The Spectrum of Hepatic Dysfunction in Inflammatory Bowel Disease. (Eng) Dew, M. J. (Nutritional and Intestinal Unit, General Hosp., Steelhouse Lane, Birmingham B4 6NH, England); Thompson, H.; Allan, R. N. *Q J Med* 48(189): 113-135; 1979.

A study of the incidence and nature of hepatic dysfunction among 1,237 patients with inflammatory bowel diseases revealed the development of biliary tree carcinoma in eight patients with longstanding total colitis. Two had been treated with panproctocolectomy many years before the onset of biliary tree obstruction. Three patients had established liver disease complicated by biliary tract carcinoma. (61 refs)

79-5913 Bilateral Wilms's Tumour in Klippel-Trenaunay Syndrome (Letter to Editor). (Eng) Ehrich, J. H. (Kinderklinik, Institut fuer Pathologie, Medizinische Hochschule Hannover, Karl Wiechert Allee 9, 3000 Hannover 61, W. Germany); Ostertag, H.; Flatz, S.; Kamran, D. *Arch Dis Child* 54(5): 405; 1979.

Bilateral Wilms' tumor in a 1-yr-old girl with the Klippel-Trenaunay syndrome is reported. At laparotomy, a nodular tumor originating from the left kidney was found, and the kidney was removed. This kidney, plus biopsy specimens taken from nodules on the right kidney, showed glomerular and tubular differentiation and solid blastomatous structures consistent with Wilms' tumor. (1 ref)

79-5914 Erythropoietin Levels in the Course of a Patient with Erythropoietin-producing Renal Cell Carcinoma and Transplantation of This Tumor in Nude Mice. (Eng) Toyama, K. (Dept. Internal Medicine, Sch. Medicine, Keio Univ., 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan); Fujiyama, N.; Suzuki, H.; Chen, T. P.; Tamaoki, N.; Ueyama, Y. *Blood* 54(1): 245-253; 1979.

Erythropoietin (EP) was measured by the exhypoxic polycythemic mouse method during the course of renal cell carcinoma associated with erythrocytosis in a 64-yr-old man. The serum EP level fluctuated with progression of the disease. The originally high level [0.11 units (U)/ml] decreased after nephrectomy and then increased again with the development of a lung metastasis (0.1 U/ml). EP was markedly increased in extracts from primary renal cell carcinoma (0.2 U/g) and lung metastasis (0.8 U/g). Cells from the lung metastasis were transplanted into nude mice, resulting in erythrocytosis in some animals. In the erythrocytotic mice, EP was elevated to levels of 0.25-0.9 U/g in the tumor tissues and 0.67 U/ml in the serum. The results indicate that the renal cell carcinoma of this patient was an EP-producing tumor. (15 refs)

79-5915 Grafts of Ehrlich's Adenocarcinoma in Normal and Hypertrophic Mouse Kidneys. (Ita) Michelazzi, A. (Istituto di patologia generale, Università di Genova, Genoa, Italy); Burlando, F. *Pathologica* 71(1012): 195-199; 1979.

Success in grafting Ehrlich's adenocarcinoma in normal and hypertrophic kidneys of Swiss mice was investigated. The results were different during the different stages of hypertrophy: positive takes were few and limited to a narrow area of the parenchyma on days 10-12 during the development of hypertrophy, but when hypertrophy had been achieved, the take rate was similar to that in normal kidneys. Tumor cells and cells that are becoming hypertrophic may compete for metabolic substrates. (1 ref)

79-5916 Hepatoblastoma with Adenomatoid Renal Epithelium. (Eng) Knowlson, G. T. (Dept. Pathology, Birmingham Children's Hosp., Ladywood Middleway, Ladywood, Birmingham B16 8ET, England); Cameron, A. H. *Histopathology* 3(3): 201-208; 1979.

A hepatoblastoma (HB) occurred in a male infant with a renal malformation involving adenomatoid epithelium lining the Bowman's capsule and the adjacent part of the proximal tubule. The infant, born after a normal full-term pregnancy without drug therapy, was mildly jaundiced at 20 hr of age; his abdomen was distended and there was hepatomegaly. The blood level of α -fetoprotein was markedly elevated at 1,280 mg/liter. The tentative diagnosis of HB was confirmed by a liver scan that showed a posterior filling defect in the right lobe. During a right lobectomy at age 5 wk, the child's blood pressure fell suddenly, he sustained cardiac arrest, and he could not be revived. The 7-cm tumor was round, well-defined, unencapsulated, and reddish in color, and it consisted histologically of rather well-differentiated liver cells.

Postmortem examination showed kidneys of normal size, but their combined wt was 45 g (normal, 34 g). Histologically, in about 50% of the glomeruli throughout the cortex, Bowman's capsule was dilated and the parietal epithelium was formed by a primitive epithelium composed mainly of columnar but, in some places, of spindle-shaped cells. This abnormal parietal epithelium extended into the adjoining part of the proximal tubules, some of which apparently had double entrances. It is concluded that HB is a malignant tumor related to developmental abnormalities. Adenomatoid transformation of the parietal glomerular epithelium may be a manifestation of aberrant development and may predispose to HB and, perhaps, other tumors. (19 refs)

79-5917 Multiple Primary Tumors in Patients with Genital Cancer. (Fre) Quereux, C. (Service de Gynécologie-Obstétrique, C.H.U., 45 rue Cognacq-Jay, 51090 Reims cedex, France); Dorangeon, P.; Wahl, P. *Gynecologie* 30(1): 74-82; 1979.

In a series of 379 patients with genital cancers, 14 had multiple cancers fulfilling the following criteria: different histology for each tumor, different organs involved, metastases appropriate to each tumor. The patients ranged in age from 49 to 67 yr. Two of the patients had tumors confined to the genital region, and six had genital cancers associated with cancers of other organs, including the breast, colon, and anus. An additional five patients had multifocal cancers of the upper genital tract, and one had multiple cancers of the lower genital tract. The cancers were diagnosed simultaneously in all but three patients, in whom the interval between the first and second cancers was 10 mo for two and 15 yr for the third. Only 6/14 patients survived for a significant period of time (4 mo to 13 yr) after diagnosis. (21 refs)

79-5918 Morphogenesis of Ovarian Cystomas. (Rus) Serov, S. F. (Lab. Pathomorphology, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Irzhanov, S. I.; Bychkov, V. M.; Zagol'skaia, V. N. *Vopr Onkol* 25(6): 29-36; 1979.

The results of a morphological examination of 1,385 serous ovarian cystoma specimens are presented. There were 467 benign, 125 intermediate, and 793 malignant cystomas; the age of the patients ranged from 18 to 82 yr. Cytophotometric analysis showed a progressive increase in ploidy from 3n in the benign tumors to 4n-7n in the intermediate tumors and 6n-10n in the malignant tumors. Electron microscope analysis revealed that the benign cystomas consisted predominantly of monomorphic cuboid cells (71%) and villous cells (18%). Malignant transformation was associated with a progressive decrease in the incidence of villous cells (to 3%-4% in intermediate cystomas) and marked cellular polymorphism. (23 refs)

79-5919 Case Report: Ultrastructure of Mature Neurogenic Implants from Ovarian Immature Teratoma. (Eng) Gonzalez-Campora, R. (Dept. Pathology, Univ. Seville Medical Sch., Seville, Spain); Nogales, F. F.; Davidson, H. G.; Mendez, J. A. *Histopathology* 3(3): 233-240; 1979.

An ultrastructural study was made of mature (Grade 0) neurogenic peritoneal implants from a Grade 1 ovarian immature teratoma. The presence of different types of neuroectodermal cells challenges the current terminology of this lesion ("gliomatosis peritonei", or peritoneal glial implants), which implies that it contains a single proliferating cell type. Light and electron microscopy demonstrated the presence of ependymal glia, central neurons, and

oligodendroglia. The ultrastructural features were indicative of maturity in all cell lines, and even the neurons exhibited well-formed synapses. Marked cytoplasmic fibrillary change, similar to that found in CNS gliosis, was observed in the astrocytes. The ependymal cells had abnormal cilia with an altered configuration and number of microtubules. (13 refs)

- 79-5920 Anterior Segment Metastases from an Ovarian Choriocarcinoma. (Eng) Frank, K. W. (Ophthalmic Pathology Lab., Kresge Eye Inst., 3994 John R St., Detroit, MI 48201); Sugar, H. S.; Sherman, A. I.; Beckman, H.; Thoms, S. *Am J Ophthalmol* 87(6): 778-782; 1979.

The case report of a 28-yr-old woman with ovarian choriocarcinoma metastatic to the anterior segment of the eye is presented. The patient developed a uveitis in the left eye; subsequently, a mass was observed in the anterior segment of that eye together with a subconjunctival mass that appeared to extend from it. Biopsy showed two different cell types consistent with the cytotrophoblastic and syncytiotrophoblastic elements typical of choriocarcinoma. (28 refs)

- 79-5921 Colpocytohistological Aspects of Uterine Condyloma. (Fre) Saurel, J. (Institut d'Histo-Cyto-Pathologie, 15 cours Georges Clemenceau, 33000 Bordeaux, France); Marc, J.; Morard, J. L.; Audebert, A. *Gynecologie* 30(2): 159-166; 1979.

The association of condyloma acuminatum of the cervix, which is due to a papilloma virus, and precancerous conditions is reviewed. From December 1977 to June 1978, 60 cases of cervical condyloma were diagnosed, usually by Papanicolaou smears. The average age of the patients was 33 yr. The condyloma cells were also found in the vagina in 4 patients, in the vulva in 1 patient, and in the endocervix in 7 patients. Cytological surveillance revealed a patient with severe dysplasia of the cervix 3 mo after the initial smear and one with carcinoma in situ at 6 mo. The histological aspects of cells in transition from the hyperkeratotic cells on the surface of the condyloma to carcinoma in situ cells are described. The "halo cell," which has a clear perinuclear halo, is characteristic of the virus-infected cells. The nuclei of these cells are sometimes enlarged, but in general they are small, prepyknotic or pyknotic, with dense, highly colored chromatin. The cytoplasm, which is lightly basophilic or eosinophilic and stains positively with orange dyes, is compressed on the periphery of the cell. According to some authors, the alteration of the halo from a perinuclear to paranuclear conformation indicates the involution of cells with malignant potential. The halo cells were found in all smears in variable numbers. (38 refs)

- 79-5922 Cervical Dysplasias. Analysis of Late Results. (Fre) Gavel, M. (Angoulême, France). *Gynecologie* 30(1): 82-84; 1979.

The occurrence of cancer in 1,915 patients treated for presumably benign lesions of the cervix is reported. The cases were gathered over a 20-yr-period (1953 to 1973). Only patients with dysplasias of the squamous or glandular epithelium or with polyps were included. Four patients developed cancer 7-13 yr after treatment for dysplasias. (no refs)

- 79-5923 Rare Lesions of the Cervix. (Fre) Minh, H. N. (Amiens, France); Smadja, A.; Coupez, F.; Lecomte, P. *Gynecologie* 30(1): 69-72; 1979.

Two patients, both age 23, with papillomas of the cervix and two patients, ages 43 and 62 with Bowen's disease of the cervix are reported. The lesions arose from the cervical malpighian epithelium. Both types of lesions are more likely to be found in the vulva or the vagina, and they have a variable potential for malignancy. (6 refs)

- 79-5924 A Case of Two Different Testicular Tumors. (Pol) Krzakowski, M. (Kliniczny Oddział Radioterapii, Centrum Kształcenia Podyplomowego WAM, ul. Szaserów 128, 00-909 Warsaw, Poland); Alexandrowicz, A.; Majkowski, J.; Nowakowski, W. *Pol Tyg Lek* 34(23): 921-922; 1979.

A malignant teratoma of the testicle was diagnosed in a 21-yr-old man. After orchiectomy, he underwent radiotherapy (total skin dose 4,500 R in 38 days). Another tumor was diagnosed in the remaining testicle 5 yr later: it was a mixed tumor composed of elements of seminoma and mature teratoma. No metastases were seen. (15 refs)

- 79-5925 Scanning Electron Microscopy of In Vitro Grown Cells from Experimentally Induced Neurogenic Tumors. (Eng) Lalitha, V. S. (17 Neelakantamehta St., T. Nagar, Madras-17, India 600017); Mennel, H. D. *Acta Neuropathol (Berl)* 47(1): 61-66; 1979.

Serially transplanted experimental neurogenic tumors were explanted in vitro and analyzed by scanning electron microscopy. The seven tumors used were induced in the offspring of pregnant BD-IX rats treated with ethylnitrosourea (single iv dose on gestation day 15) or with repeated ip doses of methylnitrosourea and estrogen. In explants of intracerebrally transplanted gliomas, small stellate cells with branching processes were observed. In transplanted tumors of the peripheral nervous system, slender bipolar cells as well as fibroblasts emerged. The stereoscopic features were compared with the features revealed by conventional light microscopy. The findings were consistent with the assumption of a glial derivation of CNS tumors induced by neurotropic alkylating carcinogens. The peripheral tumors were composed of Schwann cell-like elements and fibroblasts. (17 refs)

See also:

- *(Rev.): 79-5407, 79-5426, 79-5436, 79-5444, 79-5455, 79-5463, 79-5473, 79-5474, 79-5475, 79-5476, 79-5477, 79-5478, 79-5479, 79-5480, 79-5481, 79-5483, 79-5484, 79-5485, 79-5486, 79-5487, 79-5488, 79-5489, 79-5490, 79-5491, 79-5492, 79-5500.
 *(Chem.): 79-5512, 79-5513, 79-5524, 79-5525, 79-5530, 79-5531, 79-5534, 79-5536, 79-5537, 79-5538, 79-5540, 79-5541, 79-5548, 79-5549, 79-5550, 79-5560, 79-5561, 79-5566, 79-5569, 79-5573, 79-5575, 79-5578, 79-5587, 79-5591, 79-5603, 79-5605, 79-5610, 79-5611, 79-5630, 79-5641, 79-5644, 79-5645, 79-5664, 79-5666, 79-5668, 79-5669, 79-5672.
 *(Phys.): 79-5675, 79-5679, 79-5680, 79-5681, 79-5692, 79-5693, 79-5696.
 *(Viral): 79-5699, 79-5701, 79-5719, 79-5743, 79-5769, 79-5775, 79-5790, 79-5794.
 *(Immun.): 79-5827, 79-5840, 79-5842, 79-5846, 79-5847.
 *(Epid.-Biom.): 79-5941, 79-5942, 79-5943, 79-5953, 79-5955, 79-5958, 79-5959, 79-5963, 79-5975.

EPIDEMIOLOGY AND BIOMETRY

- 79-5926 Results of a Two-Year Determination of Nitrates in Selected Agricultural Products of Vegetable Origin. (Slo) Kirchhoffova, A. (Okresna hygienicka stanica, Leninova trieda 78, 949 01 Nitra, Czechoslovakia). *Cesk Hyg* 24(5): 251-255; 1979.

Because the high nitrate concentrations that have recently been found in vegetables may be the cause of alimentary methemoglobinemia, particularly in infants, nitrate concentrations were determined in fruits and vegetables. The nitrate concentration ranged between 5.6 and 71.2 mg/100 g, and it was higher in vegetables than in fruits. Nitrate concentrations may be influenced by the presence of nitrogen fertilizer, humidity, rainfall, and light intensity. (7 refs)

- 79-5927 Environmental Radioactivity in Greenland in 1977. (Eng) Aarkrog, A. (Riso Natl. Lab., DK 4000 Roskilde, Denmark); Lippert, J. *Riso* (388): 1-20; 1978.

Fallout radioactivity in Greenland during 1977 was measured. Strontium-90 and, in most cases, cesium-137 were determined in samples of precipitation, sea water, vegetation, animals, and drinking water. The 1977 mean levels of ^{90}Sr and ^{137}Cs in the human diet in Greenland were estimated. The ^{90}Sr level in the diet was 87% of the estimated Danish mean level, and 52% of the Faroese level. The ^{137}Cs level was 4.8 times that in the Danish diet and half that in the Faroese diet. (4 refs)

- 79-5928 Retinoblastoma in Sweden 1958-1971. A Clinical and Histopathological Study. (Eng) Kock, E. (Dept. Ophthalmology, Karolinska Hosp., Stockholm, Sweden); Naeser, P. *Acta Ophthalmol (Copenh)* 57(3): 344-350; 1979.

Retinoblastomas were diagnosed in 88 Swedish children (48 boys and 40 girls) during 1958-1971, giving an incidence of 1 case per 18,000 live births. The tumor was bilateral in 37.5% of the patients. A family history of retinoblastoma was recorded in only six cases, five of which were bilateral. All unilateral tumors were enucleated; in the bilateral cases, one eye was enucleated and the other was treated by local radiation therapy. Choroidal invasion was noted in 29% of the cases, and invasion of the optic nerve in 11%. The mortality was only 4.5%, which is considerably lower than the mortality rates reported in other Scandinavian countries. (17 refs)

- 79-5929 Menopausal Estrogen Therapy and Endometrial Cancer. (Swe) Bengtsson, L. P. (Kvinnokliniken, Lasarettet i Lund, Lund, Sweden). *Lakartidningen* 76(19): 1801-1802; 1979.

The effect of postmenopausal estrogen therapy on the incidence of endometrial cancer in Sweden was estimated from drug sales and from the estimated number of women using estrogens. Compared

with the US, the percentage of menopausal women receiving estrogen therapy is considerably lower and the duration of the treatment is substantially shorter, usually <3 yr. Based on the assumption that all menopausal women are treated with estrogens for at least 3 yr, the incidence of endometrial carcinoma would increase by an estimated 13/100,000, which means that the actual increase due to therapy is considerably lower than this estimate. Therefore, estrogen therapy at the lowest effective doses and for not >3 yr is justified for valid indications. (6 refs)

- 79-5930 Five-Year Survival and Causes of Treatment Failures in Patients with Lymphosarcoma. (Pol) Zuchowska-Vogelgesang, B. (Klinika Chemioterapii, Instytut Onkologii, ul. Garncarska 11, 31-115 Krakow, Poland); Pawlicki, M. *Nowotwory* 29(2): 115-119; 1979.

Transformation of lymphosarcoma into lymphocytic leukemia was seen in 64 patients within 5 yr of treatment (radiotherapy in all patients, and chemotherapy with Natulan, cyclophosphamide, vincristine, and vinblastine in 18). (16 refs)

- 79-5931 Leukemias at Lucknow. A Study of 200 Cases. (Eng) Kushwaha, M. R. (Lymphoma Leukemia Registry, Upgraded Dept. Pathology and Bacteriology, K. G. Medical Coll., Lucknow, India); Bagchi, M.; Mehrotra, R. M. *Indian J Cancer* 15(3): 28-34; 1978.

The frequency of leukemia and the relative incidence of different morphologic types of leukemia in Lucknow, India, were studied based on 392 cases. Chronic myeloid leukemia (CML) was the most prevalent type (56.1%), followed by acute myeloblastic leukemia (AML, 31.6%), acute lymphocytic leukemia (ALL, 8.1%), and chronic lymphocytic leukemia (CLL, 4.2%). The overall male:female ratio was 2:1, with the male predominance being most marked for CLL. Eighty percent of ALL patients were diagnosed in the first decade of life, 68% of AML patients were diagnosed in the third and fourth decades, and 73% of CLL patients were >40 yr of age. Most ALL and AML patients were urban dwellers, whereas most CLL and CML patients were rural dwellers. The incidence of leukemia in Lucknow appears to be increasing gradually. Hepatosplenomegaly, fever, bleeding episodes, and lymphadenopathy were common presenting symptoms, with the most common presenting symptom varying with morphologic type. Total WBC counts also varied with morphologic type, and the majority of AML and ALL cases had >20% blast cells in the peripheral blood. Anemia was found in the majority of the acute leukemias and in 45.6% of the CML cases. There was no definite relationship between platelet count and hemorrhagic tendency in any morphologic type. (23 refs)

- 79-5932 Lymphomas and Occupational Benzene Exposure. (Eng) Vianna, N. J. (New York State Dept. Health,

Bureau Environmental Epidemiology and Occupational Health, Albany, NY); Polan, A. *Lancet* 1(8131): 1394-1395; 1979.

A comparison was made of the 1950-1969 mortality rates for reticulum cell sarcoma, lymphosarcoma, and Hodgkin's disease among male New York state residents (excluding New York City) aged ≥ 20 yr in 14 occupations with exposure to benzene and/or other coal tar fractions and among a nonexposed control group. Relative risks were calculated for the 14 occupations based on crude death rates; for the 7 occupations for which age distributions were available (representing 80% of the total study population), age-specific death rates for each lymphoma were calculated and applied to the age distributions. The Poisson distribution was used to evaluate the significance of the findings. The relative risks based on all 14 occupations were 1.6, 2.1, and 1.6 for reticulum cell sarcoma, lymphosarcoma, and Hodgkin's disease, respectively. Within the seven occupations for which age distributions were available, the observed number of deaths was significantly higher than the expected number for each type of lymphoma. Further analysis revealed that this excess was due entirely to those men 45 yr of age or older. These results are consistent with the possibility that chronic exposure to benzene and/or other coal tar derivatives may be important in the etiology of these tumors. (15 refs)

- 79-5933 Mycosis Fungoides: Epidemiologic Observations. (Eng) Greene, M. H. (Environmental Epidemiology Branch, Field Studies and Statistics Program, NCI, NIH, Landow Building, Room C307, Bethesda, MD 20205); Dalager, N. A.; Lamberg, S. I.; Argyropoulos, C. E.; Fraumeni, J. F. *Cancer Treat Rep* 63(4): 597-606; 1979.

An analysis of cases from a multihospital, pathologically verified clinical series and of deaths from US mortality statistics at the county level for 1950-1975 (excluding 1972) was made to obtain information on the etiology of mycosis fungoides (MF). Most of the cases (85%) were in men, 64% of whom were aged 45-69 yr. One hundred and eighteen of the 211 patients reported childhood eczema, asthma, hay fever, urticaria, and/or allergies to food, drugs, and/or contact allergens. Skin disease was reported in a first-degree relative of 56 patients, and a history of cancer was reported in a first-degree relative of 63 patients. Sixty-three patients reported at least one exposure to a hazardous chemical or material and 88% of the patients were employed in manufacturing or other industries. Ninety patients reported burning easily on sun exposure, and sun sensitivity, allergy, and previous skin infections seemed closely interrelated. During 1950-1975, there were 1,948 deaths attributed to MF, the av annual age-adjusted mortality rates being 0.53×10^6 for white men, 0.28×10^6 for white women, 0.84×10^6 for nonwhite men, and 0.54×10^6 for nonwhite women. The av age-adjusted mortality rates by race and sex revealed a generally upward trend over time. The mortality rate was highest among white men in the northeastern part of the country. The influence of occupational exposures was suggested by excessive mortality rates in counties where petroleum, rubber, primary and fabricated metal, machinery, and printing industries were located. (19 refs)

- 79-5934 A Statistical Method for Testing Epidemiological Results as Applied to the Hanford Worker Population. (Eng) Brodsky, A. (P.O. 34471, W. Bethesda, MD 20034). *Health Phys* 36(5): 611-628; 1979.

A statistical method is presented for the evaluation of actual mor-

tality and longevity longitudinally over time and is preliminarily applied to previously reported data concerning the mortality experience of the Hanford worker population. A previous study had found increased radiation-produced cancer in this population. It is shown that when both employees and controls were selected from families with two or more offspring and comparisons were matched by age, sex, race and year of entry into employment, the gross mortality experience of persons employed at Hanford during 1943-1970 did not differ significantly from that of certain controls. In this method an approximate chi-square statistic for testing population subgroup comparisons is utilized, as is the cumulation of chi-squares for testing the overall result of a particular type of comparison. Some typical tables of the life-year and cumulative mortality data are presented and an explanation is given as to how the chi-square sample statistics were constructed, both for the individual subgroups and for the summed partitions of chi-square, to yield overall tests of each analysis. This method may be applicable for testing and screening in various kinds of health and population studies. (21 refs)

- 79-5935 Subacute Cadmium Intoxication in Jewelry Workers: An Evaluation of Diagnostic Procedures. (Eng) Baker, E. L. (Environmental Hazards Activity, Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Atlanta, GA 30333); Peterson, W. A.; Holtz, J. L.; Coleman, C.; Landrigan, P. J. *Arch Environ Health* 34(3): 173-177; 1979.

An outbreak of cadmium intoxication in workers in a jewelry factory is reported. Blood Cd levels in exposed workers were higher than those in unexposed workers (0.93 vs $0.38 \mu\text{g}/100 \text{ ml}$), and a dose-response relationship was noted between blood Cd level and the prevalence of four symptoms (dyspnea, chest pain, dysuria, and dizziness). No significant renal or pulmonary dysfunction was noted. Symptoms ceased after a Cd-containing brazing alloy used in jewelry production was replaced, but urine Cd levels remained elevated in four workers 1 yr later. (16 refs)

- 79-5936 A Follow-Up Study of the Geographic Distribution of Selected Malignancies Among Kentucky Residents, 1969-1976. (Eng) Sims, W. L. (Office Student Affairs, Univ. Kentucky Medical Sch., Lexington, KY 40506); Marx, M. B.; Brooks, W. H. *J Natl Med Assoc* 71(7): 685; 1979.

A study of 533 brain tumors, 339 lung tumors, and 299 breast tumors in a contiguous six-county area of Kentucky was carried out to determine if a previous clustering of brain tumors with a rate 3.37 times the rate in the rest of the state still existed. No significant difference in incidence by age, sex, or race was demonstrated between cases assignable to the six-county area and those from the entire state. (2 refs)

- 79-5937 Metastatic Brain Tumors in Two Predominantly Black Hospitals: A Statistical Analysis. (Eng) Fan, K. J. (Dept. Pathology, Howard Univ., Coll. Medicine, 520 W St. NW, Washington, DC 20059); Kovi, J. *J Natl Med Assoc* 71(7): 671-673; 1979.

A retrospective statistical analysis was done on metastatic brain tumors collected from two predominantly black hospitals in Washington, DC. A composite African series of metastatic brain tumors was also constructed for comparison. The results indicate

that bronchogenic carcinoma is the predominant metastatic brain tumor (45.2%) among the American blacks and chorio-epithelioma, the most common (20.0%) among the African blacks. In comparing these two series, much dissimilarity in the pattern of tumor distribution between these two genetically related ethnic groups suggests an important environmental role in the genesis of metastatic brain tumors. The present study also reveals a relatively high proportional frequency of prostatic carcinoma among metastatic brain tumors in blacks (3.8 percent in Washington, DC and 2.1 percent in Africa). (23 refs)

- 79-5938 Brain Tumors in Children Exposed to Barbiturates (2 Letters to Editor).** (Eng) Annegers, J. F. (Dept. Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN 55901); Kurland, L. T.; Hauser, W. A.; Gold, E. B.; Gordis, L.; Tonascia, J. A.; Szklo, M. *J Natl Cancer Inst* 63(1): 3-4; 1979.

A previous observation that children with brain tumors have a threefold increase in prior barbiturate exposure compared with that in a control population is criticized methodologically. Reasons for selecting barbiturates as a variable for the study are not given, and the types of barbiturates, duration of exposure to and the histologic types, sites, and ages at onset of the neoplasms are not fully described. The confidence intervals are large and the basic comparisons among the data are not statistically significant, which deny support for the suggested association. New data concerning barbiturate exposure and subsequent brain tumors in three cohorts exposed to anticonvulsants either in utero (1st trimester), in childhood for long periods, or as epileptic therapy are presented to further illustrate the criticisms. In a rebuttal, the authors of the original report respond to the methodological criticisms. They also state that the possibility of confounding by associated variables such as head trauma, CNS anomalies, or epilepsy may be minimal. Although the findings were only suggestive and, at most, only a small proportion of brain tumors may be attributed to barbiturate exposure, they are of sufficient interest to warrant further study in this area. (1 ref)

- 79-5939 Mortality in Aluminum Reduction Plant Workers.** (Eng) Milham, S. (Washington State Dept. Social and Health Services, Olympia, WA 98504). *J Occup Med* 21(7): 475-480; 1979.

A historical prospective (cohort) study of workers at a north-western US prebake-type aluminum reduction plant revealed a low standardized mortality ratio (SMR) for all causes of death (86), but excess deaths from lung cancer (SMR 117), pancreatic cancer (180), lymphatic and hematopoietic cancers (184), fatal benign brain tumors (391), and pulmonary emphysema (204). Analysis of mortality by job-exposure category, duration of employment, and latency suggested that some of the lymphatic and hematopoietic cancers (especially malignant lymphoma), lung cancers, and pulmonary emphysemas were of occupational origin in this population. (16 refs)

- 79-5940 Lung Cancer in Young Women.** (Eng) Jick, H. (Boston Collaborative Drug Surveillance Program, 400 Totten Pond Road, Waltham, MA 02154); Porter, J.; Morrison, A. S.; Rothman, K. J. *Arch Intern Med* 139(7): 745-746; 1979.

The cigarette smoking histories of 31 women below age 50 yr who had a diagnosis of lung cancer on hospital discharge and of 124 women below age 50 yr who had been hospitalized for other conditions were compared. Of the women with lung cancer, 28 were current or former cigarette smokers; 72 of the comparison women were smokers. The relative risk estimate for lung cancer among smokers, compared with that among nonsmokers, was 6.7, with 90% confidence limits of 4.0 and 11. Lung cancer risk increased with the amount of cigarettes that the women had smoked. The smokers with lung cancer had been smoking for longer periods than the smokers with other conditions. Assuming that the association is causal, cigarette smoking was responsible for about 77% of the cases of lung cancer found among young women in this survey. (15 refs)

- 79-5941 Relation of Steroids to Liver Oncogenesis.** (Eng) Christopherson, W. M. (Health Sciences Center, Univ. Louisville Sch. Medicine, Louisville, KY); Mays, E. T. *J Toxicol Environ Health* 5(2/3): 207-230; 1979.

Experience with pathological material from 150 women with liver tumors is reviewed. The average age of the women was 30 yr. Approx 85% had taken contraceptive steroids, most for >3 yr: 18% had taken pills containing ethinylestradiol, 64% pills containing mestranol, and 18% pills containing both preparations. The most common presenting symptom was pain; 20% presented with hemoperitoneum. The features of liver cell adenoma and focal nodular hyperplasia are sufficiently different that the vast majority of the benign tumors can be easily subclassified. Although most occurred in women ingesting steroids, the wide usage of oral contraceptives makes it difficult to prove a causative role. Nineteen patients had malignant tumors (hepatomas) and, to date, 14 have died of their disease. Since hepatomas are much more common than benign liver tumors, one must be even more circumspect in indicating steroids in their causation. None of the women had cirrhosis, whereas cirrhosis is a very common precedent lesion in the general population. Further investigation of estrogens and primary liver carcinoma is needed. (40 refs)

- 79-5942 Survey of Primary Liver Tumors and Oral Contraceptive Use.** (Eng) Vana, J. (Dept. Epidemiology, Roswell Park Memorial Inst., Buffalo, NY); Murphy, G. P.; Aronoff, B. L.; Baker, H. W. *J Toxicol Environ Health* 5(2/3): 255-273; 1979.

Survey data of the American College of Surgeons on 378 female and 165 male cases of primary liver tumor reported by 477 US hospitals during 1970-1975 are presented. In men, 91.5% of the tumors were malignant, confirming the rarity of benign liver tumors in men. Among women, 43.9% were malignant and 56.1% were benign. Of the 212 benign tumors, 96 were hepatic cell adenomas and 58 were focal nodular hyperplasias. A positive history of oral contraceptive use was found in nearly half of all tumors, 65% of benign tumors, 74% of hepatic cell adenomas, and 74% of focal nodular hyperplasias. High frequencies of benign tumors were observed in the age group 20-30 yr. More than 80% of the tumors in this age group were found in oral contraceptive users. Symptomatology was more severe among users. No case of ip bleeding was observed in nonusers. The findings confirm the suggested association between use of oral contraceptives and hepatic cell adenomas and focal nodular hyperplasias. (38 refs)

- 79-5943 Liver Cancer in the Chinese. (Ger) Wellmann, K. F. (Dept. Pathology, Beekman Downtown Hosp., 170 William St., New York, NY 10038); Gerstmann, K. E. *Disch Med Wochenschr* 104(26): 949-954; 1979.

The incidence of liver cancer among the Chinese people and its possible causes are reviewed, along with observations of patients from the Chinese section of New York City. In the US, the risk of dying of liver cancer was calculated to be 9.66 for Chinese men, 1.0 for white men, and approx 2 for black men. The risk for Chinese women living in the US was 4.31. These results are based on data collected from 1950 to 1969. Among a series of autopsies in which 15.5% of the patients were Chinese, 60% of the liver cancers were found in Chinese patients. Several studies show that the incidence of liver cancer is higher in Chinese born in China than in those born elsewhere. Thus, an environmental factor that exerts its influence early in life is suspected. Parasitic or virus infection, nutritional deficiency in childhood, and high consumption of a carcinogen (eg, aflatoxin) have been suggested. The association between liver cirrhosis (LCR) and carcinoma is closer for the Chinese people than for people of other races. In New York, 33.3% of Chinese patients with LCR had liver carcinoma, vs 4.4% of non-Chinese LCR patients. The incidence of LCR found at autopsy was 14.4% in Chinese vs 13.2% in non-Chinese subjects. The risk of liver cancer in Chinese that have had a hepatitis B infection was estimated to be 10 times that for Chinese not so infected. This increase in risk seems to be greater than that for other races. Hepatitis is very common in parts of China. It is suggested that the incidence of liver cancer might be decreased by the prevention of hepatitis. (68 refs)

- 79-5944 Malignant Neoplasms in Long-Term Hemodialysis Patients. (Eng) Fayemi, A. O. (Holy Name Hosp., 718 Teaneck Road, Teaneck, NJ 07666); Ali, M. *J Med Soc NJ* 76(7): 497-500; 1979.

The incidence of malignant neoplasms is increased in patients with chronic renal insufficiency maintained on long-term intermittent hemodialysis. A clinical and pathological study was made of 10 such patients encountered in a hemodialysis unit over the period 1969 through 1977. These patients developed 12 malignancies that were predominantly epithelial in origin: carcinomas of the thyroid (2), liver (2), colon (2), lung (1), stomach (1), kidney (1), prostate (1), and pancreas (1), and a glioblastoma multiforme. In five patients, death was attributable directly to the neoplasms. Numerous abnormalities of cellular and humoral immunity occur in uremic (and hemodialysis) patients, and they may contribute to the development of malignant tumors. (31 refs)

- 79-5945 Geographic Patterns of Renal Cancer in the United States. (Eng) Blot, W. J. (Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20205); Fraumeni, J. F. *J Natl Cancer Inst* 63(2): 363-366; 1979.

Mapping of the geographic distribution of renal cancer mortality for groupings of US counties revealed clustering of elevated rates among white men and women in the upper north-central part of the country. Throughout the US, mortality increased with urbanization for men only, whereas rates for both sexes showed positive correlations with socioeconomic status. The major correlate of the cancer rates was ethnicity. Mortality was elevated in counties with high percentages of residents of German, Scandina-

vian, and, especially, Russian descent. Ethnic susceptibility appears to account, at least partly, for the regional clustering of kidney cancer and may provide leads to environmental determinants. (19 refs)

- 79-5946 Trends in the Anatomic Distribution of Colorectal Cancer (Letter to Editor). (Eng) Welch, J. P. (Dept. Surgery, Univ. Connecticut Health Center, Farmington, CT). *Conn Med* 43(7): 457-458; 1979.

A retrospective examination of the Hartford Hospital Tumor Registry records from 1935 to 1977, revealed a persistent increase in the incidence of colorectal cancer during each succeeding decade and an increase in the incidence of cancers of the cecum and ascending colon. There was a simultaneous decrease in rectal cancer incidence. Changes in the distribution of colorectal cancer reflect, in part, the enhanced detection of more proximal tumors using colonoscopy and air-contrast barium studies and the effective removal of polyps in the rectum and lower sigmoid colon. (7 refs)

- 79-5947 Laterality of Breast Cancer in Families. (Eng) King, M. C. (Dept. Epidemiology and International Health, Univ. California, San Francisco, CA 94143); Lynch, H. T.; Selvin, S. *Am J Epidemiol* 110(1): 88-98; 1979.

A new method for analyzing concordance for a binary variable in extended pedigrees was used to study tumor laterality in 15 extended families with 63 members affected by breast cancer. Concordance and discordance measures were almost equal among these families, and there was no significant concordance for tumor laterality. However, among the Danish families of a 1948 study, concordance for tumor laterality was more than twice discordance for laterality for related breast cancer patients ($p = 0.006$). Another earlier study demonstrated significant concordance for laterality ($p < 0.05$) among twins, and the 1948 study demonstrated a nonsignificantly high concordance among siblings. The present study and a third earlier study showed a weak tendency toward discordance among sisters. Three studies indicated a tendency toward concordance for tumor laterality among parent-child pairs, but the trend was significant only in the 1948 study. The pooled data from all three studies showed a highly significant concordance among the 67 parent-child pairs ($p < 0.005$). (21 refs)

- 79-5948 Cancer of the Corpus Uteri: Increasing Incidence in the United States, 1970-1975. (Eng) Walker, A. M. (Boston Collaborative Drug Surveillance Program, Boston Univ. Medical Center, Waltham, MA); Jick, H. *Am J Epidemiol* 110(1): 47-51; 1979.

Regional and temporal variations in the incidence of cancer of the corpus uteri in the US during 1970-1975 were studied. During this period, rates for women aged 50-59 yr increased 81%, from 72 to 130 cases per 100,000 woman-yr at risk (WYAR). Rates for women aged 60-69 yr rose 57%, from 82 to 129/100,000 WYAR, and rates for women aged ≥ 70 yr increased 53%, from 45 to 53/100,000 WYAR. Despite considerable variations in incidence during the study period, the rate for women aged 40-49 yr was 31/100,000 WYAR at the beginning and end of the period. Regional variations were greatest among women aged ≥ 50 yr, especially those aged 60-69 yr. The peak incidence in the West (190/100,000) was three times that in the Northeast, which had the lowest incidence for

women aged 60-69 yr. The age of peak incidence tended to be higher in the areas of higher risk. All rates were corrected for the numbers of women in each region and age group with intact uteri. (16 refs)

- 79-5949 Endometrial Cancer in Relation to Patterns of Menopausal Estrogen Use. (Eng) Weiss, N. S. (Dept. Epidemiology, Univ. Washington, SC-36, Seattle, WA 98195); Szekely, D. R.; English, D. R.; Schweid, A. I. *JAMA* 242(3): 261-264; 1979.

The relationship between endometrial cancer and pattern of estrogen use (dose, duration, presence of an intermittent progestogen, etc) was investigated in female residents of King County, Washington, in whom endometrial cancer developed between January 1975 and April 1976. These women were interviewed concerning prior use of menopausal estrogens, and their responses were compared with those of a random sample of women from the same population. Among current estrogen users, endometrial cancer risk was strongly related to duration of use; although only a minimal elevation of risk was present during the first 2 yr, there was a rapid rise to a 20-fold excess after about 10-15 yr. Cessation of estrogen use led to a decline in the incidence of endometrial cancer within several years, but the risk remained higher than that in nonusers through the first decade after administration of the drug was stopped. Risk was elevated whether or not the regimen was cyclic and whether conjugated or other types of estrogens had been used. Dosages of <0.625 mg/day of conjugated estrogens produced a smaller increase in risk than did other dosages. (11 refs)

- 79-5950 Use of Permanent Hair Dyes and Cancer among Registered Nurses. (Eng) Hennekens, C. H. (180 Longwood Ave., Boston, MA 02115); Rosner, B.; Belanger, C.; Speizer, F. E.; Bain, C. J.; Peto, R. *Lancet* 1(8131): 1390-1393; 1979.

A retrospective evaluation was made of the possible association between the use of permanent hair dyes and cancer. The assessment also followed for any confounding effects of cigarette smoking. A 1976 survey of 120,557 married, female, registered US nurses aged 30-55 yr showed that 38,459 had at some time used hair dyes and 3,548 had had cancer. For all cancers combined, the risk ratio (RR) for the development of cancer among women who had used hair dyes at any time, compared with those who had never used them, was 1.10 ($p = 0.02$). When cancers were subdivided by anatomical site into 16 main groups, only those of the cervix uteri ($RR = 1.44$, $p < 0.001$) and those of the vagina and vulva ($RR = 2.58$, $p = 0.02$) showed statistically significant associations with the use of permanent hair dyes. Both these associations were reduced but remained significant after standardization for cigarette smoking, and neither showed increases in risk of cancer with increasing years since first use of hair dyes. Women who had used permanent dyes ≥ 21 yr before the onset of cancer had a significant increase in risk for all sites combined ($RR = 1.38$, $p = 0.02$), compared with never users. This increase was primarily due to an excess number of observed to expected cases of breast cancer (24 vs 16.3). However, among those who had first used dye 16-20 yr before the diagnosis of breast cancer, there was an almost equal deficit in number of cancers at this site (16 observed vs 25.1 expected). The present evidence does not indicate that any material risk of cancer is likely to have occurred during the initial 20 yr following the first use of permanent hair dyes. (12 refs)

- 79-5951 Vasectomy and Cancer of the Cervix (Letter to Editor). (Eng) Swan, S. H. (Kaiser-Permanente Medical Center, Walnut Creek, CA 94596); Brown, W. L. *N Engl J Med* 301(1): 46; 1979.

The relative risk of cervical cancer in women with sexual partners without vasectomies was found to be 4.29 times that among women who had partners with vasectomies ($p < 0.05$). (2 refs)

- 79-5952 Epidemiology of Cancer of the Cervix in Buffalo, New York. (Eng) Graham, S. (Dept. Sociology, State Univ. New York at Buffalo, Buffalo, NY 14261); Schotz, W. *J Natl Cancer Inst* 63(1): 23-27; 1979.

A study was made to determine whether cervical cancer patients from Buffalo and Kenmore, New York, differed from a random sample of women from the same communities on a variety of parameters associated with marital and reproductive history. A comparison of the 285 patients and 1,620 controls showed that patients were more likely than controls to have been black and non-Jewish, to have married young, to have had more than one husband, and to have been young at the time of their first pregnancy. In addition, they were more likely to have frequently used a vaginal douche and to have used it over many years. As the frequency of douching increased, so did the risk of cervical cancer. (9 refs)

- 79-5953 Discussion of Cytological Studies Performed in 1976. Conclusions. (Spa) Marhuenda Sendra, F. (No affiliation given); Medina Diez, J. M. *Rev Sanid Hig Publica (Madr)* 52(9/10): 1115-1123; 1978.

The results of 2,097 consecutive cervical and vaginal cytological examinations performed in 1976 are presented. Of 2,097 patients, 1,796 were urban and 301 provincial; 1,266 presented voluntarily, and 831 were referred. Most of the patients (1,301/2,097) belonged to the 31- to 50-yr age group. Complaints included leukorrhea (524), pain (363), and menstruation disorders or metrorrhagia (203). Six adenocarcinomas, 5 squamous cell carcinomas, 12 serious dysplasias, 142 mild dysplasias, 82 cases of mycosis, and 183 cases of trichomoniasis were diagnosed. (no refs)

- 79-5954 Mumps Virus and Ovarian Cancer. (Eng) Golan, A. (Dept. Obstetrics and Gynaecology, Baragwanath Hosp., Johannesburg, S. Africa); Joosting, A. C.; Orchard, M. E. *S Afr Med J* 56(1): 18-20; 1979.

The relationship between cancer of the ovary and mumps-neutralizing antibodies was investigated with the use of 34 ovarian carcinoma patients and controls matched for age, sex, and racial origin. Previous mumps infection was determined by interview, by complement fixation tests, and by estimations of neutralizing antibody titer. No significant differences between the two groups were found with any of the three methods used to estimate previous exposure to mumps virus. Therefore, this study did not confirm previous hypotheses that mumps infection confers a significant degree of protection against the development of ovarian cancer. A relatively small proportion of cases could possibly be due to a lack of such protection, but in this study the max possible is 30% at a fiducial limit of 5%. (19 refs)

- 79-5955 The Epidemiology of Ovarian Carcinoma. (Ger) Wolnik, L. (Universitäts-Frauenklinik, Pilgrimstein 3, D-3350 Marburg 1, W. Germany); Bauer, H. *Onkologie* 2(2): 96-101; 1979.

A study of 190 women with ovarian cancer treated during 1962-1976 showed that this group contained a high percentage of childless women and women with more than four children. A high social standing, blood group A, obesity, diabetes, high blood pressure, uterine polyps, a previous appendectomy or laparotomy for other causes, and several relatives with cancer were also found to be risk factors. (50 refs)

- 79-5956 Breast Cancer Incidence: Geographical Correlations in Finland. (Eng) Hakama, M. (Finnish Cancer Registry, Liisankatu 21 B, 00170 Helsinki 17, Finland); Soini, I.; Kuosma, E.; Lehtonen, M.; Aromaa, A. *Int J Epidemiol* 8(1): 33-40; 1979.

An attempt was made to determine whether geographical differences in fertility factors and in standard of living in Finland account for the observed geographical differences in breast cancer incidence rates. Breast cancer risk was found to be associated with fertility and taxable income but not with the size of the woman. Trends in risk factors indicate that the rapid increase in the incidence of breast cancer is likely to continue. It is concluded that factors that are reflected by the standard of living and fertility might act independently and not through the nutritional status, for which the size of the woman is an operational indicator. (20 refs)

- 79-5957 An Epidemiological Study of Oral Contraceptives and Breast Cancer. (Eng) Vessey, M. P. (Univ. Dept. Social and Community Medicine, Oxford OX1 3QN, England); Doll, R.; Jones, K.; McPherson, K.; Yeates, D. *Br Med J* 1(6180): 1757-1758; 1979.

From 1968 to 1977, 707 women aged 16-50 yr with newly diagnosed breast cancer and 707 matched controls were interviewed at eight teaching hospitals in London and Oxford about their use of oral contraceptives (OC). Eighty-six of the breast cancer patients were matched with controls with gallbladder disease; these subjects were omitted from the main analyses, which thus related to 621 case-control pairs. A few statistically significant differences in OC use were found between the breast cancer and control groups, but the data were subdivided in many ways, so that some "significant" differences would have been expected to occur by chance. The only subgroup in which the evidence for a positive association between OC use and breast cancer was convincing comprised women aged 46-50 yr, but trends in those aged 41-45 were by and large in the opposite direction, and the results of combined analyses gave no cause for concern. Information on clinical stage was available for 487 breast cancer patients treated before the end of 1975. Those who had never used OC had appreciably more advanced tumors at presentation than those who had been using OC during the year before detection of the lump; while past users of OC occupied an intermediate position. This difference in staging was reflected in the pattern of survival. OC may have had a beneficial effect on tumor growth and spread, although diagnostic bias could not be definitely excluded. (no refs)

- 79-5958 Results of Rectoscopic Studies of Unselected Patients. (Ger) Veres, R. (Klinik Hochstaußen, Postfach 13, D-

8232 Bayerisch Gmain, W. Germany); Berghoff, A. *Med Klin* 74(12): 449-452; 1979.

Unsuspected rectal carcinomas were found in 7/1,665 unselected patients (>45 yr old) with common internal disorders that were studied rectoscopically. Only two of these tumors were palpable. At least 1 polyp was found in 304/1,665 patients; 126 of these had the histological criteria of premalignancy. Rectoscopy is recommended for the regular screening of patients at internal medicine clinics. (13 refs)

- 79-5959 Etiology of Human Liver Cancer: Controlled Prospective Study in Liver Cirrhosis. (Eng) Lehmann, F. G. (Dept. Medicine, Univ. Marburg, Marburg/Lahn, W. Germany); Wegener, T. *J Toxicol Environ Health* 5(2/3): 281-299; 1979.

The incidence of primary hepatocellular carcinoma (PHCC) was investigated in a 77-mo prospective study of 403 clinically unselected patients derived from a homogeneous population by serial determination of α_1 -fetoprotein (AFP) with the use of radioimmunoassay. The diagnosis of liver cirrhosis was proved in 90% by laparoscopy and/or histology and/or autopsy. The incidence of PHCC in liver cirrhosis in the clinically studied patients was 4.47%, significantly lower than that in the autopsy material (11.03%; $p \leq 0.025$). In the follow-up study, all patients with increasing AFP concentrations exhibited a PHCC. A transitory rise of AFP (>50 nanograms/ml) was observed in 15.1% of patients with liver cirrhosis without PHCC. In contrast to the results of animal experiments, this transitory rise of AFP was not followed by malignant transformation of the cirrhotic tissue. Posthepatic liver cirrhosis was observed in 21.57%, postalcoholic liver cirrhosis in 42.93%, and cryptogenic liver cirrhosis in 27.30%. Liver cirrhosis of other etiology occurred in 8.19%. The incidences of PHCC in these four groups were 4.94%, 4.62%, 5.45%, and 0%, respectively. These differences are not statistically significant, although in absolute figures, postalcoholic liver cirrhosis was the main cause of PHCC in this sample from West Germany. Hepatitis B surface antigen (HBsAg)-positive liver cirrhosis was more often associated with PHCC than HBsAg-negative liver cirrhosis (6.58% vs 3.96%); this difference also is not statistically significant. Observations of larger groups of patients may show a higher risk of developing PHCC in those with a combination of alcohol abuse and HBs antigenemia and/or acute hepatitis in their history. Patients without these two risk factors had a 2.61% incidence of PHCC; those with one risk factor, 5.77%; and those with both risk factors, 10.71%. (55 refs)

- 79-5960 Epidemiological Study of Carcinoma of Liver in the Dodoma Region of Tanzania. (Eng) Hiza, P. R. (Muhimbili Medical Centre, Univ. Dar es Salaam, P.O. Box 20693, Dar es Salaam, Tanzania). *J Natl Med Assoc* 71(6): 585-587; 1979.

Because primary hepatocellular carcinoma (PHC) is common in Africa and because the disease probably has an environmental etiology, a study was undertaken in Dodoma, Tanzania, to obtain baseline data on PHC prior to the improvement in hygiene and diet that are likely to occur. These baseline data may help pinpoint the causative factors in PHC. Of the 939 patients diagnosed as having cancer at any of the four Dodoma regional hospitals, 27% had PHC, a high incidence by all standards. Of 141 patients interviewed at these hospitals, 88% consumed ground nuts either daily

or weekly, and 50% of these respondents ate the nuts after storage. There were 124 regular consumers of ground nuts and 17 non- or occasional consumers. In addition, 49% of the consumers but only 18% of the non- or occasional consumers had a positive history of jaundice, a finding that is statistically significant. The significance of these findings in relation to PHC is not clear. It appears that regular ground nut consumption affects the liver so as to make it more susceptible to hepatitis. The effect may be due to hepatotoxins in the nuts that damage the liver and make it more susceptible to hepatitis B virus infection. (3 refs)

- 79-5961 Carcinoma of the Esophagus. (Eng) Ajao, O. G. (Dept. Surgery, Univ. Ibadan and Univ. Coll. Hosp., Ibadan, Nigeria); Solanke, T. F. *J Natl Med Assoc* 71(7): 703-705; 1979.

Carcinoma of the esophagus, previously thought to be rare in West Africa, is now known to be relatively common in Ibadan. In a 39-mo period, extending from January 1975 to March 1978, 30 cases of esophageal carcinoma were seen on the surgical service of one hospital. Males were affected more than females (2.3:1), and the highest incidence was found in the sixth and seventh decades of life. Of the 30 patients, 23 belonged to the low and 7 to the low-middle socioeconomic classes. The predominant histological type was squamous cell carcinoma (90%), with the remainder being adenocarcinoma; the most common site was the lower third of the esophagus (51.85%), followed by the midthoracic esophagus (29.6%). Surgical resection is recommended when feasible, even as a palliative measure. (12 refs)

- 79-5962 Cohort Analysis of Lung Cancer in the Netherlands. (Eng) Van Der Hoff, N. M. (Peeskesweg 3, Beek Gem., Bergh, Netherlands). *Int J Epidemiol* 8(1): 41-47; 1979.

A mathematical method was used to analyze lung cancer mortality in the Netherlands from 1963 to 1974. A multiplicative model was fitted to a two-dimensional table of age- and cohort-specific rates. Apart from small corrections, age-specific lung cancer mortality rates could be expressed as the product of a cohort (generation) factor and an age factor. The cohort factors increased until the 1930 birth cohort, after which there was a rapid decline. The age-risk factors increased gradually with age. Age-specific incidence curves for past and future years will follow the curve of the age-risk factors, provided that the cohort-risk factors do not change. The method can be applied to other chronic diseases. (8 refs)

- 79-5963 Relationship Between Clinical Findings and Histology of Primary Lung Cancer. (Jpn) Kobara, Y. (Second Dept. Medicine, Chest Disease Res. Inst., Kyoto Univ., Kyoto, Japan); Sato, A.; Matsui, Y.; Imai, H.; Honda, K.; Oshima, S. *Bull Chest Dis Res Inst Kyoto Univ* 12(1/2): 17-27; 1979.

The relationship between cigarette smoking and lung cancer was confirmed in a study of 728 patients (578 men, 150 women). There were 290 men and 39 women with epidermoid carcinoma, 146 and 76 with adenocarcinoma, 137 and 27 with undifferentiated carcinoma, and 5 and 8 with alveolar cell carcinoma, respectively. Among the cigarette smokers (342 men, 64 women), 173 men and 15 women had epidermoid carcinoma, 82 and 31 had adenocarcinoma, and 87 and 18 had undifferentiated carcinoma. The smokers were classified according to the Brinkman Index (BI =

number of cigarettes smoked/day x total years smoking). A person with a BI of >400 is considered a heavy smoker. There was an especially large number of heavy smokers with epidermoid carcinoma and undifferentiated carcinoma and a lower number of heavy smokers with adenocarcinoma. A BI of >600 was found in 132/173 men with epidermoid carcinoma and 71/87 men with undifferentiated carcinoma. The occurrence of adenocarcinoma was significantly higher among nonsmokers than smokers, and there were significantly fewer women smokers than men. There was a correlation between cigarette smoking and the incidence of epidermoid and undifferentiated carcinoma. (17 refs)

- 79-5964 Cancer in the Aged: An Autopsy Study of 940 Cancer Patients. (Eng) Ishii, T. (Dept. Pathology, Keio Univ. Sch. Medicine, 35 Shinanomachi, Shinjuku-Ku, Tokyo 160, Japan); Maeda, K.; Nakamura, K.; Hosoda, Y. *J Am Geriatr Soc* 27(7): 307-313; 1979.

Among 1,366 patients aged 65 or older autopsied between 1955 and 1977, 940 were found to have one or more cancers (total, 1,030 cancers). The prevalence rate for overall cancer declined after age 85 in men and after age 75 in women. The chief sites of major cancers were the stomach, lung, esophagus, liver, and pancreas, in that order. Incidental cancers (chiefly of the prostate, thyroid, and colon) were found more often in patients >80 yr old. For multiple primary cancers, the prevalence rate was relatively constant until the age of 70, when it rose to a peak in the 80-84 age group before declining to the original level. (26 refs)

- 79-5965 Diet and Cancer. (Eng) Hirayama, T. (Epidemiology Div., Natl. Cancer Center Res. Inst., Tokyo, Japan). *Nutr Cancer* 1(3): 67-81; 1979.

Data from a series of Japanese studies concerning the effect of diet on cancers of the lung, esophagus, stomach, colon, breast, and cervix are reviewed. The risk of lung cancer in smokers and nonsmokers was reduced by consumption of green-yellow vegetables (GYV), and among ex-smokers, reduction in lung cancer risk with time after cessation of smoking was greater among those who consumed GYV daily than among others. Vitamin A must be the most important factor in any protective effect of GYV, followed by vitamin C. GYV consumption had a similar, but weaker effect on colon, stomach, and prostate cancers. The risk of esophageal cancer was increased in those who smoked and consumed alcohol, the risk increasing with the alcohol content of the beverage consumed. The risk of esophageal cancer was also increased by the combined intake of bracken fern and hot tea gruel. Stomach cancer was lowest in persons consuming two glasses of milk daily, and the amount of fiber consumed was negatively correlated with colon cancer mortality. Daily meat intake had no effect on colon cancer risk, but daily meat consumption was associated with increased breast and pancreatic cancer risks. Breast cancer mortality was positively correlated ($r = 0.842$) with daily fat intake. The risk of cervical cancer was negatively correlated ($r = -0.855$) with vitamin A intake. (17 refs)

- 79-5966 Gastrointestinal Disorders. Patients seen During 1977 in an Internal Medicine Clinic Oriented Toward Hepatogastroenterology. (Fre) Bockel, R. (Service de medecine interne III, gastro-enterologie, Clinique medicale B, C.H.U. Strasbourg, France); Schneider, R.; Saada, K.; Doffoel, M.; Girard, M.; Coumaros, D. *Arch Mal Prof* 40(1/2): 216-221; 1979.

Clinical findings were compared for 444 immigrants and 984 native French subjects with gastrointestinal disorders seen in a hospital and outpatient clinic during 1977. No neoplasms were diagnosed in the immigrants, but 34 neoplasms (4 esophageal, 5 gastric, 11 hepatic, 4 pancreatic, and 10 colorectal tumors) were found in the native French patients. (no refs)

79-5967 Incidence of Gastrointestinal Cancers in a Well-defined French Population. Survey of Registration Data in the Cote d'Or for 1976-1977. (Fre) Faivre, J. (Registre des cancers digestifs, Faculte de Medecine, 7 bd Jeanne-d'Arc, 21033 Dijon Cedex, France); Keppling, C.; Martin, F.; Cabanne, F.; Michiels, R.; Dusserre, P. *Rev Epidemiol Sante Publique* 27(1): 41-49; 1979.

The results of a systematic registration of the mortality and morbidity from gastrointestinal (GI) cancer in the Cote-d'Or, France (population, 455,727), during 1976 and 1977 are reported. In this 2-yr period, there were 692 deaths from GI cancer, and 913 new cases were reported. The site most likely to be involved was the colorectal area (246 deaths and 444 new cases), followed by the stomach (148 deaths and 174 new cases); the site least likely to be involved was the small intestine (3 deaths and 7 new cases). The incidence of cancer of the esophagus and intestine rose sharply after age 45; that of cancer of the stomach, liver, and pancreas rose sharply after the age of 50. Cancers of the esophagus were most likely to be squamous cell carcinomas (71%) whereas cancers in other GI sites were almost always adenocarcinomas. The mortality rate 1 yr after registration was 80% for cancers of the esophagus, 71% for primary cancers of the liver, 67% for cancers of the stomach and the pancreas, 45% for cancers of the colon, and 32% for cancers of the rectum. (8 refs)

79-5968 Changes in Mortality Due to Carcinoma of the Stomach in France Between 1954 and 1974. (Fre) Brunet, M. (Division de la Recherche Medico-Sociale, INSERM, Section Cancer, 44 chemin de Ronde, 78110 Le Vesinet, France); Berlie, J.; Janin, M. L.; Zimmermann, B.; Hucher, M.; Ducourneau, R. *Nouv Presse Med* 8(21): 1743-1744; 1979.

Changes in mortality due to carcinoma of the stomach in France between 1954 and 1974 were studied on the basis of probable levels standardized for the French population in 1968. There was a marked decline in mortality for both sexes. In men, the 1954 level was 54.8/100,000, and the decrease was of the order of 1.35 deaths/100,000/yr, an annual decrease of 3.21%. This phenomenon was more marked during the second period (1965-1974), than during the first period (1954-1963), with the decreases amounting to 3.88% and 2.38%, respectively. In women, the initial mortality rate was 31.25/100,000, and the annual decrease was 3.49%. The fall was 3.09% for the first 10-yr period and 4.80% during the second period. Thus, in France, as in many other countries, there has been a marked decrease in mortality due to carcinoma of the stomach. (no refs)

79-5969 Mortality due to Bladder Cancer in France, 1952-1976. Trends and Increase, Particularly in the South of France. (Fre) Berlie, J. (Centre Rene Huguenin, 5 rue Gaston-Latouche, F 92210 Saint-Cloud, France); Janin, M. L.; Hucher, M.; Gest, J.; Brunet, M. *Bull Cancer (Paris)* 66(3): 317-326; 1979.

Data on bladder cancer mortality in France during 1952-1976 were analyzed statistically to determine whether there were any relationships between this mortality and sex, age, or geography. Among men, the mortality rate increased from 3.8/100,000 in 1952 to 9.2/100,000 in 1976; the corresponding figures for women were 2.06/100,000 and 3.30/100,000. The annual increase was 2.65% among men and 1.34% among women, so that in 1976, the age-adjusted mortality rate was 11.35/100,000 men and 3.20/100,000 women. When mortality was analyzed by birth cohorts, absolute levels for the age group 70-79 yr increased from 41.1 for the population born before 1900 to 47.5 for the following generation. Computerized mapping of the geographical distribution of bladder cancer showed a significant predominance in the south of France and a highly significant correlation with the geographical distribution of lung and gallbladder cancer mortality in France. (10 refs)

79-5970 Epidemiological Study of 314 Cases of Cancer of the Bladder in the Administrative Department of Bas-Rhin, France. (Eng) Bollack, C. (Service de Chirurgie Urologique, C.H.U., Strasbourg, France); Poyot, G. *Urol Res* 7(2): 127-130; 1979.

The geographical distribution of 314 cases of bladder cancer among eight districts of the Department of Bas-Rhin in France was studied. Considerable variations in morbidity were observed, with an urban predominance possibly due to environmental factors. The av morbidity in two districts was 7.3 cases/100,000 residents, which was similar to the av for the Department as a whole. In two other districts, the av morbidities were 10 and 8.5 cases/100,000 residents, respectively, and in four districts the av was between 5.9 and 6.1 cases/100,000 residents. Among 180 patients studied more extensively, nine (5%) had second tumors diagnosed before, at the same time as, or shortly after the diagnosis of bladder cancer. Of five such patients with second tumors of the lung, pharynx, or mouth, five were heavy smokers. (11 refs)

79-5971 Cancers of the Ethmoid in Woodworkers. (Fre) Haguenaer, J. P. (Institut universitaire de medecine du travail de Lyon, Lyon, France); Bourret, J.; Duclos, J. C.; Dubreuil, C.; Arnould, G. *Arch Mal Prof* 40(1/2): 422-423; 1979.

Among a series of 55 patients with adenocarcinomas or other malignant tumors of the ethmoid diagnosed since 1972, 23 were woodworkers. The av age at the time of diagnosis was 55-60 yr, and the duration of exposure was 15-30 yr for 7, 30-40 yr for 7, and >40 yr for 3 patients; 6 were diagnosed after retirement. Most of the woodworkers were exposed to wood dust. (no refs)

79-5972 A Multicenter Inquiry into the Etiology of Pancreatic Diseases. (Eng) Sarles, H. (INSERM U 31, 46 Chemin de la Gaye, F-13009 Marseille, France); Cros, R. C.; Bidart, J. M. *Digestion* 19(2): 110-125; 1979.

The etiology of pancreatic diseases and the diet of patients with these diseases were surveyed with the collaboration of 36 centers in 19 countries having widely different climatic and racial conditions. A total of 2,478 patients were studied: 222 men and 208 women with acute pancreatitis (AP), 801 men and 134 women with calcified chronic pancreatitis (CCP), 525 men and 155 women with noncalcified chronic pancreatitis (NCCP), 69 men and 14 women with pancreatic cancer, and 281 male and 62 female controls. With

regard to chronic pancreatitis, the 19 countries could be classified into 4 dietary groups. (1) Southern Europe: the diet is rich in carbohydrates, protein, and lipids; alcohol intake is primarily in the form of wine; and the pathology is dominated by CCP. There are fewer women than men with chronic pancreatitis. (2) Northern Europe, Argentina, and Chile: the diet is rich in protein and alcohol consumption is beer-based, and there is a distinct prevalence of AP and NCCP. The prevalence of men with chronic pancreatitis is less marked than that in southern Europe. (3) Japan: the diet is poor in lipids and there is a low frequency of CCP and NCCP. (4) Tropical countries with mixed races that can be divided into two subclasses: (a) India is characterized by a low-fat, low-protein diet; no alcoholism; a high frequency of CCP at an early age; (b) Brazil and South America are characterized by a very high alcohol intake in the form of whiskey and a high frequency of CCP. (32 refs)

79-5973 Lung Cancer in Iron Miners in Lorraine. 270 New Cases Observed from 1964-1977. (Fre) Anthoine, D. (Service de pneumologie, Centre medical Paul Spillmann, 54690 Lay Saint-Christophe, France); Lamy, P.; De Ren, G.; Braun, P.; Cervoni, P.; Petiet, G.; Schwartz, P.; Zuck, P.; Lamaze, R. *Arch Mal Prof* 40(1/2): 48-51; 1979.

Characteristics of the lung cancer observed in 270 iron miners of Lorraine, France during the period 1964-1977 are presented. The cancers were more likely to be discovered by screening than those of nonminers and the lesion was more likely to be distal in location. Other literature studies presenting statistics on the incidence of lung cancer in iron miners are reviewed. (4 refs)

79-5974 Malignant Mesotheliomas in a Small Village in the Anatolian Region of Turkey: An Epidemiologic Study. (Eng) Artvinli, M. (Dept. Chest Diseases, Hacettepe Univ., Sch. Medicine, Ankara, Turkey); Baris, Y. I. *J Natl Cancer Inst* 63(1): 17-22; 1979.

Epidemiologic and etiologic studies of malignant pleural mesotheliomas (MPM's) were performed in two small villages in

the Anatolian region of Turkey, Tuzkoy and Kizikoy (the latter was used as a control). People ≥ 25 yr of age were studied, 312 (145 men and 167 women) from Tuzkoy and 95 (45 men and 50 women) from the control village. The annual incidence of MPM in Tuzkoy was found to be 6.5 cases (22 cases/10,000 people). Several other respiratory disorders were detected as well. Although no type of asbestos could be found in or around Tuzkoy, the asbestiform mineral zeolite was found in soil samples from its roads and fields, in its building stones, and in lung tissues of the villagers. Chest x-rays revealed no cases of MPM or other respiratory abnormalities in the control group. No zeolite could be found in the control village. Therefore, zeolite is thought to be the cause of MPM and the other respiratory disorders in Tuzkoy. (14 refs)

79-5975 Pleural Asbestosis in Dock Workers. (Ger) Diwok, K. (Klinik fur Innere Medizin, Wilhelm-Pieck Univ., Ernst-Heydemann-Strasse 6, DDR-25 Rostock, E. Germany); Lutkeholter, G.; Wendel, H.; Schleue, E.; Mucke, H. *Z Gesamte Inn Med* 34(7): 76-77; 1979.

During the last 3 yr, 29 patients with pleural asbestosis were examined. Twenty-one of them had a history of occupational exposure to dust. The beginning of exposure was at least 15 yr ago, and the duration of exposure was 5-25 yr. Two bronchial carcinomas and one pleural mesothelioma were found, which emphasizes the increased risk of malignancy among asbestosis patients. (13 refs)

See also:

*(Rev.) 79-5408, 79-5413, 79-5428, 79-5430, 79-5431, 79-5433, 79-5435, 79-5437, 79-5439, 79-5440, 79-5441, 79-5442, 79-5443, 79-5450, 79-5452, 79-5480, 79-5484, 79-5493, 79-5494, 79-5495, 79-5496, 79-5497, 79-5498, 79-5500, 79-5501, 79-5502, 79-5503, 79-5504, 79-5505, 79-5506, 79-5507, 79-5508, 79-5509, 79-5510.

*(Chem.): 79-5527, 79-5596, 49-5601, 79-5605, 79-5645, 79-5671.

*(Phys.): 79-5689, 79-5690, 79-5694.

*(Path.): 79-5853, 79-5888, 79-5909.

MISCELLANEOUS

- 79-5976 Export of Proteins from Oocytes of *Xenopus laevis*. (Eng) Colman, A. (Dept. Biological Sciences, Univ. Warwick, Coventry CV4 7AL, England); Morser, J. *Cell* 17(3): 517-526; 1979.

Experiments designed to test the specificity of protein secretion by oocytes of *Xenopus laevis* are described. When human lymphoblastoid messenger RNA (mRNA) was microinjected into *X. laevis* oocytes, interferon titers rapidly reached a max inside the oocyte but accumulation of interferon continued in the incubation medium for at least 45 hr. If interferon protein was injected into oocytes, it was rapidly inactivated. Significantly, newly synthesized interferon but not injected interferon was found to be membrane-associated. Further experiments involving the coinjection of mRNA's coding for secretory proteins (guinea pig milk proteins and human interferon) and nonsecretory proteins (rabbit globin) revealed that only the secretory proteins were exported from the oocyte. Moreover, different proteins were exported at different rates. A distinct subclass of newly synthesized oocyte proteins of unknown function also accumulated in the incubation medium. Since the information encoded in the mRNA's of secretory proteins is sufficient to specify the synthesis, compartmentation, and secretion of these proteins, the oocyte may provide a complete system for the analysis of the secretory process. (42 refs)

- 79-5977 Relationships among Purine Nucleoside Metabolism, Adenosine Triphosphate Catabolism, and Glycolysis in Human Erythrocytes. (Eng) Henderson, J. F. (Dept. Biochemistry, McEachern Lab., Univ. Alberta Cancer Res. Unit, Edmonton, Alberta T6G 2H7, Canada); Zombor, G.; Burrige, P. W.; Barankiewicz, G.; Smith, C. M. *Can J Biochem* 57(6): 873-878; 1979.

In human RBC incubated with both naturally occurring purine nucleosides and with a variety of purine nucleoside analogs, ATP catabolism was accelerated and lactate accumulation was increased. Tubercidin was a particularly potent inducer of ATP catabolism. In cells incubated with tubercidin, the major route of adenylate metabolism was deamination, whereas in cells incubated with deoxyglucose, the major route was dephosphorylation. (20 refs)

- 79-5978 Xanthine Oxidase Activity in Extracts from Contact-inhibited and Spontaneously Transformed Mouse Embryo Cells in Culture. (Eng) Clynes, M. M. (Dept. Zoology, Univ. Coll., Belfield, Dublin 4, Ireland); Shannon, M. F.; Hurley, M. P. *Biochem Soc Trans* 7(3): 524-525; 1979.

The spontaneously transformed mouse cell lines 3T12 (derived from BALB/c mouse embryos) and 3T6 (from noninbred Swiss mouse embryos) were found to have higher xanthine oxidase activity than their contact-inhibited normal counterparts, BALB/3T3 and 3T3 cells. Nonconfluent BALB/3T3 and 3T12 cells contained lower xanthine oxidase activity than did confluent cells. (13 refs)

- 79-5979 Effects of Proteases and Protease Inhibitors on the 4.5 S and 8 S Androgen Receptor. (Eng) Wilson, E. M. (Dept. Pediatrics, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC 27514); French, F. S. *J Biol Chem* 254(14): 6310-6319; 1979.

The size of the cytoplasmic and nuclear androgen receptors from Sprague-Dawley rat ventral and dorsal prostate, dorsal prostate (Dunning) tumor, testis, epididymis, and seminal vesicle was determined by Sephadex G-200 chromatography and sucrose gradient centrifugation. The protease inhibitor diisopropyl fluorophosphate (DFP) was used to minimize receptor breakdown. An 8S-9S, 8S- to 106-A receptor (mol wt = 280,000 to 365,000; frictional ratio f/f_0 = 1.9 to 2.4) observed in unfractionated cytosol prepared in low ionic strength buffer with or without DFP was in equilibrium with a 4.5S-5S, 58-A form (mol wt = 117,000; f/f_0 = 1.8) observed at salt concentrations >0.1 M KCl. Receptor partially purified using $(\text{NH}_4)_2\text{SO}_4$ or phosphocellulose chromatography in the absence of DFP was present as smaller fragments of 3.6S, 37A and 3.0S, 23A. Similar fragments were generated from the 4.5S or 8S receptor by mild trypsin treatment. In addition, ventral prostate contained a DFP-insensitive enzyme that specifically converted the 4.5S, 58-A receptor to the 3.6S, 37-A fragment. The DFP-insensitive enzyme was partially inhibited by rabbit bile, and it appeared similar to the enzyme seminin, a secretory protein of human prostate. Androgen receptor isolated in the presence of DFP from nuclei labeled in vivo was predominantly 4.5S, 58 A, with smaller forms (37 and 23 A) appearing in the absence of DFP. The 4.5S, 58-A nuclear receptors were also in equilibrium with a large 8S form. Receptor breakdown by DFP-insensitive and -sensitive proteases appeared to be an in vitro phenomenon. Furthermore, the size of the androgen receptor was not significantly changed during receptor migration from cytoplasm to nucleus. (57 refs)

- 79-5980 Characterization and Biosynthesis of ω -Aminoacyl Amino Acids from Rat Brain and the C-6 Glioma Cell Line. (Eng) Bauer, K. (Abt. Biochemie, Max-Volmer-Institut, Technische Universität Berlin, Franklinstrasse 29, D-1000 Berlin 10, W. Germany); Salnikow, J.; de Vitry, F.; Tixier-Vidal, A.; Kleinkauf, H. *J Biol Chem* 254(14): 6402-6407; 1979.

Omega-Aminoacyl acids from rat brain and the C-6 glioma cell line were isolated and characterized. Extracts of the glial cell line and of rat brain were separated in an ion-exchange chromatography system fitted with a stream splitter and continuously monitored after alkaline hydrolysis and reaction with o-phthalaldehyde for amino acids and peptides. Amino acid analysis of the fractionated material before and after acid hydrolysis indicated the presence of several peptides. When the ω -amino acid-containing fractions were further analyzed, carnosine [N-(β -alanyl)histidine], homocarnosine [N $^{\alpha}$ -(γ -aminobutyl)histidine], N $^{\alpha}$ -(β -alanyl)lysine, and N $^{\alpha}$ -(γ -aminobutyl)lysine were detected in the rat brain extract. In the glioma cell extract, N $^{\alpha}$ -(β -alanyl)ornithine and N $^{\alpha}$ -(γ -aminobutyl)ornithine, but not the corresponding lysine derivatives, were identified in addition to carnosine and homocarnosine. When the glioma cells

were incubated with the radiolabeled precursors β -alanine, γ -aminobutyric acid, and ornithine, label was incorporated into these peptides. For the β -alanyl-radiolabeled material, cochromatography with the synthetic peptides carnosine and N^{α} -(β -alanyl)ornithine was demonstrated in several chromatographic systems, and after acid hydrolysis, [3 H] β -alanine was found to be a constituent amino acid. Although carnosine has been discussed as a putative neurotransmitter of the olfactory chemoreceptor neurons, these results demonstrate that carnosine and related peptides are not only present in the C-6 glial cell, but they are actively formed by these cells. (23 refs)

- 79-5981 Transcription of Ti Plasmid-derived Sequences in Three Octopine-Type Crown Gall Tumor Lines. (Eng) Gurley, W. B. (Plant Disease Resistance Res. Unit, Agricultural Res., U.S. Dept. Agriculture, Madison, WI 53706); Kemp, J. D.; Albert, M. J.; Sutton, D. W.; Callis, J. *Proc Natl Acad Sci USA* 76(6): 2828-2832; 1979.

Transcription of tumor-inducing (Ti) plasmid-derived sequences was studied in two sunflower tumor lines and a tobacco tumor line induced by *Agrobacterium tumefaciens* strains 15955, B6, and B6-806, respectively. Total RNA isolated from the three octopine-type crown gall lines contained sequences homologous to specific regions of the Ti plasmid of *A. tumefaciens* strain 15955. A comparison of transcripts in these three tumor lines suggests that tumor cells transcribe various sequences within a sector of plasmid DNA of 13×10^6 daltons and that transcription may not be uniform across the plasmid-derived sequences (T-DNA). Transcription of T-DNA by octopine-type tumors occurred at four major sites. The levels of transcription occurring at three of these sites appeared to vary considerably among the three tumor lines. Part of this variability may reflect differences in the organization and copy number of T-DNA. One of the transcription sites mapped within a region of DNA with common sequence homology to all Ti plasmids. Varying amounts of transcript homologous to this region of T-DNA were present in all three tumor lines. It is suggested that transcription of these conserved sequences in the plant may have significance regarding the mechanism of tumorigenesis. (33 refs)

- 79-5982 Tumor-specific DNA Sequences in Shay's Granulocytic Sarcoma. (Jpn) Yokoyama, S. (Dept. Medicine, Showa Univ. Sch. Medicine, Tokyo, Japan); Tsuruoka, N. *Acta Haematol Jpn* 42(3): 347-356; 1979.

DNA-RNA hybridization experiments were conducted to detect unique DNA sequences in Shay's granulocytic sarcoma cells, which was used as a model of human leukemia. Repetitive sequences comprised 47% of the tumor cell DNA, nonrepetitive sequences 53%. At low C_{ot} , the hybridization of tumor DNA with 3 H-uridine-labeled tumor RNA was higher than the hybridization of normal liver DNA with 3 H-uridine labeled tumor RNA. This indicated that abnormal sequences were present in the repetitive base sequence of tumor DNA. Poly G-C sequences were increased in the repetitive sequences of the tumor DNA. Compared with normal cell DNA, there were no abnormal sequences in the nonrepetitive sequence of the tumor DNA. Since the sarcoma contained high levels of reverse transcriptase activity, it is suggested that the abnormal sequences found in the repetitive base sequences of the tumor DNA originated from viral sources. (53 refs)

- 79-5983 Spontaneous Transformation and Prolonged In Vitro Maintenance of Fetal Mouse Glial Cells. (Fre) Coulomb, B. (Section de Biologie, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex 05, France); Levy, S.; Maunoury, R.; Markovits, P. *Bull Cancer (Paris)* 66(3): 229-234; 1979.

Six cell lines obtained from the whole brain, cortex, or brain stem of A/Jax or C3H mice on gestation day 14 were maintained in culture and tested regularly for tumorigenicity in nude or syngeneic mice. The cells retained their glial character for about 1 mo after seeding. All cells were tested by the immunoperoxidase method for the presence of glial fibrillary acidic protein (GFAP). When 10^6 cells were injected into nude, A/Jax, or C3H mice, only the 14A cell line from the whole brain of an A/Jax mouse induced tumors in the syngeneic strain. Transformation occurred in the 11th cell generation. GFAP was detected in 14A cells from the whole brain, including the tumor cells and the cortex cells, but not in the brain stem cells. (15 refs)

- 79-5984 Differentiation of Human Neuroblastoma Cells in Culture. (Eng) Littauer, U. Z. (Dept. Neurobiology, Weizmann Inst. Science, Rehovot, Israel); Giovanni, M. Y.; Glick, M. C. *Biochem Biophys Res Commun* 88(3): 933-939; 1979.

The neuronal properties of a human neuroblastoma cell line (CHP-134) were found to be modulated to a high degree as a function of time in culture, even without the use of external inducing agents. A membrane glycoprotein, approx mol wt 200,000, was modulated in concert with an active ionic flux in the presence of 2% dimethyl sulfoxide. Other neuronal properties, acetylcholinesterase and choline acetyltransferase activity, were also modulated but to a lesser extent. The activity of these enzymes was independent of inducing agents. The appearance of the membrane glycoprotein on the surface of both human and mouse neuroblastoma cells only under conditions of differentiation leads to the suggestion that it is directly involved with active Na^+ channels. The finding that the cultured CHP-134 cells, which maintained their tumorigenicity, also showed a high degree of neuronal characteristics suggests that the concept that highly differentiated cells lose their tumor potential should be reconsidered. (14 refs)

- 79-5985 Diagnosis of Intraocular Tumors by the Radiophosphorus Test. (Ger) Schmitt, E. J. (Univ. Augenklinik Mainz, Mainz, W. Germany). *Klin Monatsbl Augenheilkd* 174(3): 408-410; 1979.

Experience with the use of the radiophosphorus test as an additional method for diagnosing intraocular tumors is reported. In 49 cases, there was a 90% agreement between the positive test results and the histological findings. (no refs)

- 79-5986 Inhibition of the Activity of DNA Polymerase α by 2',3'-Dideoxythymidine 5'-Triphosphate. (Eng) Ono, K. (Lab. Viral Oncology, Aichi Cancer Center Res. Inst., Chikusa-Ku, Nagoya 464, Japan); Ogasawara, M.; Matsukage, A. *Biochem Biophys Res Commun* 88(4): 1255-1262; 1979.

A low concentration (1 μ M) of 2',3'-dideoxythymidine 5'-triphosphate (ddTTP) strongly inhibited (>70%) the activity of DNA polymerase α from MOPC-104E mouse myeloma cells in the

presence of Mn^{2+} . This activity was not inhibited in the presence of Mg^{2+} , even with up to 50 μM ddTTP. The extent of inhibition could be increased by raising the pH of the reaction. The inhibition was found to be caused by competition between ddTTP and 2'-deoxythymidine 5'-triphosphate for the same substrate binding site on the enzyme. The K_i for ddTTP (0.035 μM) was much lower than the K_m for ddTTP (1.8 μM). These findings indicate that ddTTP can be used to identify DNA polymerase α and to study the mechanism of in vitro DNA synthesis. (13 refs)

79-5987 Stress and Coping Factors Influence Tumor Growth. (Eng) Sklar, L. S. (Dept. Psychology, Carleton Univ., Ottawa, Ontario K1S 5B6, Canada); Anisman, H. *Science* 205(4405): 513-515; 1979.

The effects of stress (escapable or inescapable shock applied for 6 sec at 1-min intervals, 1.1-3.3 hr/day, 1-10 days) and coping mechanisms on the development of tumors following sc injection of syngeneic P815 mastocytoma cells were studied using male DBA/2J mice. Mice exposed to only one session of inescapable shock 24 hr after tumor implantation showed significantly earlier tumor appearance ($p < 0.01$), greater tumor area ($p < 0.001$), and earlier mortality ($p < 0.001$) than nonshocked controls. Tumor size was significantly greater ($p < 0.001$) and tumor latency was significantly shorter ($p < 0.05$) among animals exposed to inescapable shock than among those able to escape shock; mortality was nonsignificantly earlier among the mice exposed to inescapable shock. Compared with mice exposed to inescapable shock for 5 or 10 consecutive days, those shocked for only 1 day showed significantly reduced tumor latency ($p < 0.001$), significantly increased tumor size ($p < 0.001$), and significantly reduced survival time ($p < 0.001$). The data support the hypothesis that stress is involved in the development of carcinoma. (14 refs)

79-5988 Demonstration of Low Density Lipoprotein Receptors in Mouse Teratocarcinoma Stem Cells and Description of a Method for Producing Receptor-deficient Mutant Mice. (Eng) Goldstein, J. L. (Dept. Molecular Genetics, Univ. Texas Health Science Center, Dallas, TX 75235); Brown, M. S.; Krieger, M.; Anderson, R. G.; Mintz, B. *Proc Natl Acad Sci USA* 76(6): 2843-2847; 1979.

An attempt was made to devise a practical scheme for producing, from developmentally versatile mouse teratocarcinoma stem cells, whole-animal models with lesions comparable to familial hypercholesterolemia, a human genetic disorder that entails a deficiency in the specific cell-surface receptor that binds low-density lipoprotein (LDL) with a consequent alteration in the control of cholesterol metabolism. This requires first learning whether the tumor stem cells in culture express LDL receptors and then establishing a selection or screening procedure to identify receptor-deficient mutants in mutagenized cell cultures. The results show that the teratocarcinoma cells do in fact have specific high-affinity LDL receptors that are similar to those reported for fibroblasts and the parenchymal cells of specialized tissues and different from those of phagocytic cells. Sterols suppressed the otherwise efficient binding, internalization, and degradation of LDL (^{125}I -labeled) by the cells. Acetylation of LDL blocked the binding. Only LDL and not high-density lipoprotein (HDL) was bound. After LDL uptake and degradation, the liberated cholesterol led, as expected, to increased cholesteryl ester formation; it also suppressed the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step in cholesterol biosynthesis. Cells with LDL receptors

were readily visualized by exposing them to a fluorescent derivative of LDL; in the fluorescence microscope, labeling was seen in all cells. Cells with experimentally depressed receptors, yielding little fluorescence, were separable from those with normal fluorescence. Thus, two methods for isolating receptor-deficient cells from mutagenized cultures are now available, either by visual recognition of low-fluorescing or nonfluorescing colonies in culture plates or by electronic cell sorting. Such mutants in an appropriate line of teratocarcinoma cells can then be passaged into blastocysts for full somatic tissue differentiation and germ-line development into mice. (26 refs)

79-5989 Teratocarcinoma Stem Cells Have a Cell Surface Carbohydrate-binding Component Implicated in Cell-Cell Adhesion. (Eng) Grabel, L. B. (Dept. Anatomy, Univ. California, San Francisco, CA 94143); Rosen, S. D.; Martin, G. R. *Cell* 17(3): 477-484; 1979.

The presence of a carbohydrate-binding component on the surface of teratocarcinoma (TC) stem cells was demonstrated. TC stem cells maintained in the undifferentiated state expressed a carbohydrate-binding component that recognized oligomannosyl residues. This cell-surface molecule was detected by a rosette assay in which the stem cells formed rosettes with glutaraldehyde-fixed trypsinized rabbit RBC. Addition of simple sugars to the assay mixture had little effect, but rosette formation was inhibited by a series of mannose-rich glycoproteins (yeast invertase, yeast mannan, and horseradish peroxidase). Periodate oxidation eliminated the inhibitory activity of invertase, whereas pronase digestion had little effect, indicating that carbohydrate moieties are essential for inhibition. Invertase and its glycopeptide derivatives also inhibited the reaggregation of dispersed stem cells and promoted the dissociation of preformed aggregates. These results suggest that intercellular adhesion of TC stem cells may be the consequence of the interaction of a lectinlike component detected in the rosette assay with a complementary oligosaccharide receptor on adjacent cells. (38 refs)

79-5990 The Differentiation of Teratocarcinoma Stem Cells Is Marked by the Types of Collagen Which Are Synthesized. (Eng) Adamson, E. D. (Dept. Zoology, Univ. Oxford, South Parks Road, Oxford, OX1 3PS, England); Gaunt, S. J.; Graham, C. F. *Cell* 17(3): 469-476; 1979.

Collagen synthesis was studied in a cloned line of undifferentiated teratocarcinoma cells (OC15S1) maintained as a homogeneous embryonal carcinoma (EC) cell population or cultured under conditions in which the cells differentiated into endodermlike (END) cells. Cell cultures were incubated with tritiated proline and lysine, and the radioactive collagen secreted into the medium was extracted and purified or immunoprecipitated by antibodies to type IV collagen. Radioactive collagens were identified by electrophoretic mobility, sensitivity to collagenase and to reduction, insensitivity to pepsin, cyanogen bromide peptides, and by amino acid analyses of 3-hydroxyproline, 4-hydroxyproline, and proline. OC15S1 EC cells synthesized several collagenous polypeptides, 60%-70% of which were like that of basement membrane (type IV) collagen. Type I-like collagen was the main collagenous product of END cells, but a minor product of EC cells. It was concluded that type IV collagen synthesis was suppressed during the differentiation of EC cells to END, but type I-like synthesis was increased. Similarly, other EC cell lines produced mainly type IV-like collagen polypeptides (PC13, F9, PSA1); following the formation of

END cells, two lines produced mainly type I-like collagen polypeptides (PC13, C145b). The type of endoderm formed on embryoid bodies, however, presents an alternate route of differentiation, since immunoperoxidase tests showed that it was synthesizing significant amounts of type IV collagen. (35 refs)

- 79-5991 Comparison of a Human Tumor Cell Line Before and After Growth in the Nude Mouse. (Eng) Fogh, J. (Human Tumor Cell Lab., Sloan-Kettering Inst. Cancer Res., Rye, NY); Bean, M. A.; Bruggen, J.; Fogh, H.; Fogh, J. M.; Hammar, S. P.; Kidera, Y.; Loveless, J. D.; Sorg, C.; Wright, W. C. In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 215-234; 1978.

Several investigators participated in a study of the MeWo human melanoma cell line before and after passage in the nude mouse. Cells from a cultured line (NuCuMeWo) established after passage of the MeWo tumor were identical in morphology, ultrastructure, growth pattern, growth rate, susceptibility to poliovirus, and isozyme phenotypes to the original MeWo tumor. The modal chromosome number (44) was also the same before and after passage in the nude mouse, and various chromosome abnormalities were present in both MeWo and NuCuMeWo cells. The tumor histopathologies of both lines were similar, as were their tumor-producing capabilities in nude mice. As target cells in human lymphocyte-mediated cytotoxicity assays, MeWo and NuCuMeWo behaved similarly; in immune adherence tests, the two cell lines were similar but not identical. Thus, it appears that human tumor cell lines can be grown in vivo in the nude mouse and then again in vitro with little change in various parameters. (40 refs)

- 79-5992 Aging of Melanocytes. (Eng) Hu, F. (Div. Cutaneous Biology, Oregon Regional Primate Res. Center, Beaverton, OR 97005). *J Invest Dermatol* 73(1): 70-79; 1979.

The aging of choroidal melanocytes was studied using the eyes from rhesus monkey (*Macaca mulatta*) fetuses, neonates, infants, adolescents, young adults, and old adults. Melanocytes from biopsy samples of human lentigo simplex, lentigo senilis (LS); multiple lentiginos syndrome (MLS); nevus spilus (NS); junctional (JN), compound, and id nevus (IN); lentigo maligna (LM); and superficial malignant melanoma were also studied. With advancing age, the choroidal melanocytes showed the following changes: a tendency for the melanosomes to fuse into complexes; uneven melanization; melanolysosomes in the form of vacuoles containing irregular fibrillary or myelinlike lamellated membranes; and lipidlike granules completely or partially filled with homogeneous material of minimal electron density. The percentage of melanocytes with such changes was 10%-15% at 7 yr, 50% at 13 yr, and >60% at 15 yr. LS tissues showed a slight elongation of the rete ridges, an increase in the concentration of melanocytes in the basal layer, an increase in the amount of melanin in the melanocytes and basal keratinocytes, and melanin-containing macrophages in the dermis. In the tissue of MLS or NS, there were, in addition, a few giant melanosome complexes containing up to hundreds of melanosomes bound by a single membrane. These changes were exaggerated in LS. The ultrastructure of JN cells was similar to that of melanocytes in lentiginos. In IN, the nevus cells immediately below the dermoepidermal junction resembled JN cells, but deeper in the dermis they lost their proliferative and melanogenic activity. A wide variety of changes was

seen in LM melanosomes, many of the changes being similar to those seen in lentiginos. The data show that ultrastructural changes in melanosomes of postmitotic, fully differentiated choroidal melanocytes are quantitatively and qualitatively related to aging. (21 refs)

- 79-5993 Evidence for Removal at Different Rates of O-Ethyl Pyrimidines and Ethylphosphotriesters in Two Human Fibroblast Cell Lines. (Eng) Bodell, W. J. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Singer, B.; Thomas, G. H.; Cleaver, J. E. *Nucleic Acids Res* 6(8): 2819-2829; 1979.

The extent of removal and the relative persistence of O-ethylpyrimidines and ethylphosphotriesters (EPT) from replicating normal (GM637) and xeroderma pigmentosum (XP-12 RO) cells were investigated in an attempt to learn more about the specificity and diversity of enzymes acting presumably as glycosylases or dealkylases. Seven ethyl derivatives were induced in these cells by using ¹⁴C-ethylnitrosourea, and their removal and persistence were assayed chromatographically. Both GM637 and XP-12 RO fibroblasts had similar abilities to remove ethyl products (approx 34% and 27% were lost from these cells, respectively), except for O⁶-ethylguanine (OEG), which persists longer in the XP-12 RO cells. The absolute amounts of O²-ethylthymine (O²-ET), (O⁴-ET), and O²-ethylcytosine (OEC) were decreased in cellular DNA after correction for cell growth. The rate of decrease diminished after approx 20 hr, and 20%-40% of each derivative persisted after more than two cell doublings. Because these derivatives are stable in isolated DNA, the decreases observed in vivo are attributed to enzymatic activity. The unstable purine derivatives 7-ethylguanine and 3-ethyladenine were removed from cellular DNA at a faster rate than they disappeared in vitro, and this rate cannot be accounted for by the lability of the glycosyl bond. Again, the results imply enzyme activity in the removal of these derivatives. The amount of EPT remained almost unchanged during 72 hr of cell culture, implying that their removal involves a unique mechanism. The persistence of O²-ET, O⁴-ET, OEC, and OEG may be explained in at least two ways: (1) an enzyme capable of removing alkyl products is present or induced in early replication and is no longer active after a certain period of time, or (2) the protected alkyl derivatives are in a chromatin subfraction protected from enzymes and excised either more slowly or not at all. Their persistence during replication and transcription may represent initiating events in carcinogenesis. (39 refs)

- 79-5994 The Influence of Implantation Site on Tumor Growth and Blood Flow. (Eng) Young, S. W. (Dept. Radiology, Stanford Univ. Medical Center, Stanford, CA 94305); Hollenberg, N. K.; Abrams, H. L. *Eur J Cancer* 15(5): 771-777; 1979.

A study was made of the differences in tumor growth and their relationship to tumor blood flow in several different tissues. A suspension of V2 carcinoma cells was implanted in the liver, spleen, kidney, testicle, and ear of 34 New Zealand white rabbits. Two weeks after implantation, blood flow in the tumor and surrounding normal host tissue was determined with radioactive microspheres. Total tumor wt was found to be related to the site of implantation: liver (8.7 g), spleen (8.4 g), kidney 2.9 g, testicle (1.2 g), and ear (0.4 g). The amount of gross caseous necrosis in the V2 carcinoma was also related to implantation site. The organ with the largest proportion of grossly nonnecrotic tumor was the

liver (5% necrotic) and that with the least was the spleen (62% necrotic). V2 blood flow also varied with implantation site, the highest flow being found in the kidney (1.3 ml/g/min) and the lowest in the ear (0.14 ml/g/min). Regression analysis revealed that tumor blood flow was directly related to resting blood flow in the surrounding host parenchyma. However, no relationship existed between tumor perfusion and either tumor size or the amount of central necrosis. (22 refs)

- 79-5995 Flow Cytometry of Isolated Nuclei Prepared from 9L Rat Brain Tumor. (Eng) Hoshino, T. (Brain Tumor Res. Center, Dept. Neurological Surgery, Univ. California, 350 Parnassus Ave., Suite 807, San Francisco, CA 94143); Gray, J. W.; Nomura, K. *Lab Invest* 41(1): 72-76; 1979.

A modification of a previously reported nucleus isolation procedure is described in detail. Nuclei isolated by grinding 9L rat brain tumors gave a DNA distribution consisting of a diploid (2C) DNA peak due to noncycling normal cells and a bimodal distribution beginning at about 4C DNA due to cycling tumor cells. Autoradiographic studies of nuclei from rats that received a pulse of ^3H -thymidine in vivo confirmed that the majority of proliferating cells were in the bimodal part of the distribution. The fraction of cells in the S phase, determined from the DNA distributions, was 15.3%. This is consistent with a labeling index of 18%, determined from autoradiographs of tumor tissue, and an S-phase fraction of 17%, determined by analysis of a fraction of labeled mitosis (assuming that all of the 53% noncycling cells are in G_0). Autoradiographic analysis of cells sorted from the tumor's mid-S-phase region showed that only 58% of these cells were labeled. This is attributed mostly to the presence of fluorescent debris from necrotic nuclei in this part of the distribution. (17 refs)

- 79-5996 Population Analysis of the DNA Content in Adenocarcinoma Cells by Means of Flow Micro-Fluorometry. (Eng) Nishiya, I. (Dept. Obstetrics and Gynecology, Sch. Medicine, Hokkaido Univ., Sapporo, Japan); Ishizaki, Y. *Proc Japan Acad., Series B: Phys & Biol Sci* 55(2): 53-57; 1979.

Cellular DNA levels in 3 cases of undifferentiated cervical adenocarcinoma (AC), 6 cases of moderately differentiated endometrial AC, and 3 cases of serous ovarian cystadenocarcinoma were studied by rapid flow microfluorometry. All three cervical and five of the endometrial AC's demonstrated two peaks: the second peak arose in the diploid area and the first arose in the tetraploid to hexaploid ranges. The ovarian cystadenocarcinomas showed a narrow, sharply pointed peak in the diploid range. At the same time, there was a wide distribution among the samples ranging from the tetraploid to the hexaploid areas. (8 refs)

- 79-5997 Inhibition of Mammary Tumorigenesis in GR Mice with 2-Bromo- α -ergocryptine. (Eng) Welsch, C. W. (Dept. Anatomy, Michigan State Univ., E. Lansing, MI 48824); Goodrich-Smith, M.; Brown, C. K.; Wilson, M. *Int J Cancer* 24(1): 92-96; 1979.

An attempt was made to determine if prolactin is a contributing hormone in the genesis of mammary tumors in GR mice. In one series of experiments, 238 15-wk-old nulliparous GR mice were

treated with estrone (0.5 mg/liter drinking water) plus progesterone (30-mg pellet with cholesterol, implanted sc once monthly) for 13 wk. Half of these mice were inoculated sc once daily with 100 μg of the prolactin-suppressing drug 2-bromo- α -ergocryptine (CB-154) for the duration of hormone treatment, and the other half were inoculated sc once daily with 0.9% NaCl soln (controls). In another series of experiments, 87 pregnant GR mice were divided into two groups and inoculated sc once daily from days 7 to 21 of pregnancy with 0.9% NaCl soln (controls) or CB-154 (100 μg /mouse). In the first series, the number of mice with mammary tumors and the total number of mammary tumors were: controls, 58/119 and 73; CB-154-treated, 34/119 and 37, respectively. In the second series, the numbers were: controls, 39/44 and 73; CB-154-treated, 24/43 and 43, respectively. In both studies, CB-154 treatment significantly reduced the percentage of mice with mammary tumors and the total number of mammary tumors ($p < 0.05$ - 0.005). These results provide evidence that prolactin contributes to the genesis of estrone/progesterone- and pregnancy-induced mammary tumors in female GR mice. (31 refs)

- 79-5998 Ceruloplasmin Elevation and Synthesis in Rats with Transplantable Tumors. (Eng) Linder, M. C. (Dept. Chemistry, California State Univ., Fullerton, CA 92634); Bryant, R. R.; Lim, S.; Scott, L. E.; Moor, J. E. *Enzyme* 24(2): 85-95; 1979.

Plasma ceruloplasmin (CP) levels were measured in adult female rats of three strains with various transplantable tumors. Ceruloplasmin oxidase (CO) activity in the plasma of most tumor-bearing rats was significantly elevated over that in controls by 25%-200%. The degree of elevation showed some correlation to tumor size, especially in the case of the larger tumors, and elevations were not evident in animals with one of the slowest growing tumors. Removal of the adrenal glands did not modify the effect of tumor implantation on CO levels. Within 6 days after implantation of the fast-growing tumor line DMBA-5A, CP activity was increased an additional 50% by 21 days. The elevation in CO activity was accompanied by an increase in plasma copper concentrations. Both CO and copper increased to the same degree in the initial phase of tumor growth; however, CO activity continued to increase as the tumors grew much larger, whereas copper did not. The incorporation of (^3H)leucine into all plasma protein classes was depressed in the tumor-bearing animals, but the incorporation into CP was increased appreciably. The state of activation of CP from tumor-bearing rats was greater than that of CP from normal controls. CP activation was well correlated with CO activity in individual rats with mammary tumors. (19 refs)

- 79-5999 Clinical and Pharmacological Implications of Cancer Cell Differentiation and Heterogeneity. (Eng) Calabresi, P. (Dept. Medicine, Brown Univ., Roger Williams General Hosp., 825 Chalkstone Ave., Providence, RI 02908); Dexter, D. L.; Heppner, G. H. *Biochem Pharmacol* 28(12): 1933-1941; 1979.

Various aspects and interrelationships of intraneoplastic diversity were investigated at two levels: (1) differences among multiple subpopulations of tumor cells at any point in time (heterogeneity) and (2) variations among these subpopulations as a result of their maturation with time (differentiation). Cancer cells obtained from BALB/c/c3H murine mammary tumors and a transplantable rhabdomyosarcoma passaged in CE/J mice, as well as from two

patients with carcinoma of the colon were used. Several cell lines of these tumors were cloned and characterized. Neoplastic cell differentiation was induced by the polar solvent N,N-dimethylformamide (DMF). Differentiation was evidenced by morphological maturation, conversion of tumor cell markers and cell culture characteristics to those consistent with a more benign phenotype, and loss of tumorigenicity. Striking morphological and biological heterogeneity was observed in neoplastic subpopulations isolated from a single tumor, including marked variability in growth potential, surface antigens, and sensitivity to chemotherapeutic agents. The ability to dissect and analyze tumor cell heterogeneity in human cancer with this methodology offers a unique opportunity to delve into the clinical and pharmacological implications of tumor substructure. (33 refs)

79-6000 Glycoproteins of Cultured Epithelial Cells from Human Colonic Adenocarcinoma and Fetal Intestine. (Eng) Kim, Y. S. (Gastrointestinal Res. Lab., Veteran Admin.

Hosp., 4150 Clement St., San Francisco, CA 94121); Whitehead, J. S.; Perdomo, J. *Eur J Cancer* 15(5): 725-735; 1979.

The mol wt distribution and Concanavalin A binding properties of labeled glycopeptides and glycoproteins from cell surface membranes, cytoplasmic fractions, and culture media were studied in human fetal and neoplastic colonic cells. The cells were cultured in the presence of [^{14}C]- or [^3H]-labeled glucosamine or fucose. Both fucose and glucosamine were incorporated into the membrane glycoprotein fraction of colonic adenocarcinoma cells to a much lesser extent than into fetal cells. The elution profile obtained from Bio-gel P-150 column chromatography indicated that colonic cancer cell membranes contained fucose- and glucosamine-labeled, trypsin labile, high mol-wt glycopeptides not present in fetal cells. Affinity chromatographic studies of membrane glycopeptides using agarose-bound Concanavalin A indicated that cell membranes from fetal and colonic cancer cells contained not only glycoproteins of different mol wt, but glycoproteins having different oligosaccharide side chains. These results indicate that there are significant quantitative and qualitative differences in cell surface glycoproteins between fetal and cancerous intestinal cells. (29 refs)

Author Index

- Aarkrog, A., 79-5927
 Aaronson, S. A., 79-5758
 Abeyounis, C. J., 79-5835
 Abrams, H. L., 79-5994
 Adams, A., 79-5780
 Adams, E. F., 79-5595
 Adams, S. L., 79-5716
 Adamson, E. D., 79-5990
 Adamson, J. W., 79-5859
 Adelman, M., 79-5534
 Adler, I. D., 79-5693
 Ageenko, A. I., 79-5808
 Aizawa, T., 79-5791
 Ajao, O. G., 79-5961
 Albert, M. J., 79-5981
 Albright, J., 79-5630
 Aleksandrov, V. A., 79-5570
 79-5635
 Alexander, L., 79-5891
 Alexandrowicz, A., 79-5924
 Ali, M., 79-5944
 Allan, R. N., 79-5912
 Allen, J. R., 79-5616
 Alwine, J. C., 79-5716
 Ametov, A. S., 79-5662
 Andersen, K. S., 79-5541
 Andersen, P. R., 79-5757
 Anderson, R. G., 79-5988
 Anderson, R. S., 79-5648
 Anderson, T., 79-5542
 Andersson-Anvret, M., 79-5781
 Anikin, I. V., 79-5853
 Anisimov, V. N., 79-5635
 Anisman, H., 79-5987
 Annanmaki, M., 79-5679
 Annegers, J. F., 79-5938
 Anthoine, D., 79-5973
 Anthony, P. P., 79-5491
 Antoniolli, D. A., 79-5668
 Anzil, A. P., 79-5666
 Aoyama, Y., 79-5841
 Archambault-Couture, L., 79-5846
 Argyropoulos, C. E., 79-5933
 Arnould, G., 79-5971
 Aromaa, A., 79-5956
 Aronoff, B. L., 79-5942
 Arora, H. L., 79-5619
 Arrand, J. R., 79-5786
 Arthur, L., 79-5731
 Arthur, L. O., 79-5735, 79-5766
 Artvinli, M., 79-5974
 Arvanitakis, C., 79-5853
 Astaldi, G., 79-5844
 Astrin, S. M., 79-5699
 Atkins, D., 79-5511
 Atterwill, M., 79-5730
 Audebert, A., 79-5921
 Aurelian, L., 79-5776
 Avery, R. J., 79-5750
 Awa, A. A., 79-5681
 Axelsson, O., 79-5498
 Ayras, P., 79-5614
 Azocar, J., 79-5761
 Bach, F. H., 79-5463
 Bacigalupo, A., 79-5861
 Baden, J. M., 79-5525
 Bader, M., 79-5495
 Baetcke, K. P., 79-5615
 Bagchi, M., 79-5931
 Baillieu, E., 79-5905
 Baim, A. S., 79-5852
 Bain, C. J., 79-5950
 Baker, E. L., 79-5935
 Baker, H. W., 79-5942
 Bakotin, J., 79-5907
 Ball, J. K., 79-5728
 Baltimore, D., 79-5737, 79-5822
 Bansal, B. R., 79-5547
 Bansal, S. C., 79-5547
 Barankiewicz, G., 79-5977
 Barbacid, M., 79-5758
 Barberis, M., 79-5869
 Baris, Y. I., 79-5974
 Barlow, S. M., 79-5437
 Baron, M. H., 79-5822
 Bartsch, H., 79-5526
 Basak, S., 79-5755
 Bashkaev, I. S., 79-5808
 Batjer, K., 79-5450
 Batrakova, V. P., 79-5698
 Battifora, H. A., 79-5887
 Batzinger, R. P., 79-5581
 Bauer, H., 79-5955
 Bauer, K., 79-5980
 Baxter, S. R., 79-5663
 Bean, M. A., 79-5991
 Beaudry, C., 79-5846
 Becci, P. J., 79-5643
 Becker, B., 79-5875
 Beckman, H., 79-5920
 Beiss, B., 79-5825
 Belanger, C., 79-5950
 Belianchikova, N. I., 79-5756
 Ben-Efraim, S., 79-5820
 Benard, Y., 79-5892
 Bence, J., 79-5520
 Bend, J. R., 79-5652
 Bengtsson, L. P., 79-5929
 Benjamin, S. A., 79-5684
 Bennett, M., 79-5455, 79-5462
 Benson, A. M., 79-5604
 Bentvelzen, P., 79-5821
 Benz, R. D., 79-5851
 Berger, U., 79-5777
 Berghoff, A., 79-5958
 Berk, A. J., 79-5813
 Berkow, R. L., 79-5859
 Bertie, J., 79-5968, 79-5969
 Berman, J. J., 79-5550
 Bern, H. A., 79-5669
 Bernal, E., 79-5538
 Bernard, S. R., 79-5697
 Bertana, C., 79-5857
 Bertoldo, U., 79-5898
 Beschke, G., 79-5876
 Bhatt, T. S., 79-5977
 Biaglow, J. E., 79-5592
 Bibbo, M., 79-5671
 Bibor-Hardy, V., 79-5773
 79-5775
 Bice, D., 79-5533
 Bidart, J. M., 79-5972
 Binger, M. H., 79-5814
 Bishop, J. M., 79-5713
 Bishop, R., 79-5894
 Bisighini, G., 79-5860
 Bjursell, G., 79-5768
 Blangy, D., 79-5787
 Blank, M. A., 79-5711
 Blot, W. J., 79-5945
 Boaz, J., 79-5750
 Bochkov, N. P., 79-5530
 Bockel, R., 79-5966
 Bodell, W. J., 79-5568, 79-5993
 Boecker, B. B., 79-5684
 Boeva, M., 79-5808
 Bogaars, H. A., 79-5884
 Bogaert, M. D., 79-5609
 Bolis, P. F., 79-5850
 Bollack, C., 79-5970
 Bolognesi, C., 79-5565
 Bolt, H. M., 79-5528
 Bondi, A., 79-5860
 Boobis, A. R., 79-5518
 Boranic, M., 79-5460
 Bornstein, P., 79-5712
 Borsa, J., 79-5687
 Bos, R. P., 79-5580
 Bourdais, J. P., 79-5897
 Bourdeau, P., 79-5429
 Bourret, J., 79-5971
 Boyse, E. A., 79-5823
 Bracken, W. M., 79-5633
 Bradfield, J. W., 79-5548
 Bradley, M. O., 79-5542
 Brady, L. W., 79-5449
 Braendli, B., 79-5443
 Brajkovich, I. E., 79-5595
 Brande, I., 79-5840
 Branca, H., 79-5907
 Braun-Falco, O., 79-5881
 Braun, P., 79-5973
 Braun, W., 79-5545
 Bresnick, E., 79-5621
 Bridges, J. W., 79-5552
 Brodie, M. J., 79-5518
 Brodsky, A., 79-5419, 79-5683
 79-5934
 Bromley, P. A., 79-5717
 Bronsino, E., 79-5898
 Brooks, W. H., 79-5936
 Brown, C. C., 79-5643
 Brown, C. K., 79-5997
 Brown, D. L., 79-5557
 Brown, G. B., 79-5594
 Brown, M. C., 79-5847, 79-5848
 Brown, M. S., 79-5988
 Brown, S., 79-5715
 Brown, W. L., 79-5951
 Bruggen, J., 79-5991
 Brunet, M., 79-5968, 79-5969
 Bruszewski, J. A., 79-5747
 Bryant, R. R., 79-5998
 Buchmann, E., 79-5858
 Buchner, S., 79-5864
 Budinger, J. M., 79-5594
 Bueding, E., 79-5581, 79-5600
 79-5604
 Buening, M. K., 79-5634
 Buic, S., 79-5876
 Bulpitt, C. J., 79-5518
 Bunato, E., 79-5898
 Bunte, H., 79-5488
 Bunyan, P. J., 79-5529
 Buratto, B., 79-5538
 Burke, L., 79-5668
 Burlando, F., 79-5915
 Burm, A. G., 79-5524
 Burrage, P. W., 79-5977
 Busk, L., 79-5608
 Busse, E., 79-5632
 Butler, W. H., 79-5619
 Button, M., 79-5885
 Bychkov, V. M., 79-5918
 Byers, M. J., 79-5750
 Cabanne, F., 79-5967
 Caillard, J. F., 79-5892
 Cairns, J., 79-5589
 Calabresi, P., 79-5999
 Calcaterra, T. C., 79-5868
 Callahan, R. M., 79-5742
 Callis, J., 79-5981
 Calvieri, S., 79-5857
 Cameron, A. H., 79-5916
 Canaani, D., 79-5795, 79-5796
 Carbone, F., 79-5882
 Carlesimo, O. A., 79-5857
 Carlsson, H. W., 79-5862
 Carr, I., 79-5865
 Carr, J., 79-5865
 Carrara, M., 79-5695
 Carter, D. M., 79-5692
 Castagna, M., 79-5625
 Casto, B. C., 79-5640
 Cervoni, P., 79-5973
 Cesarone, C. F., 79-5565
 Cha, Y. M., 79-5604
 Cha, Y. N., 79-5600
 Chakarvarti, S. K., 79-5694
 Chan, S. L., 79-5883
 Chandra, P., 79-5765
 Chardonnet, Y., 79-5812
 Chasles, J., 79-5892
 Chen, C. B., 79-5414
 Chen, C. L., 79-5544
 Chen, T. P., 79-5914
 Chenciner, N., 79-5794
 Chesebro, B., 79-5743
 Chiarelli, P., 79-5695
 Chimenti, S., 79-5857
 Chimishkian, K. L., 79-5756
 Chirikjian, J. G., 79-5705
 Cho, H. Y., 79-5746
 Chou, M. W., 79-5631
 Chow, Y. L., 79-5409
 Christensen, W. L., 79-5747
 Christopherson, W. M., 79-5941
 Chuang, A. H., 79-5621
 Ciciliot, V., 79-5896
 Clairmont, A. A., 79-5478
 Clark, C. G., 79-5505
 Clark, H. F., 79-5757
 Clark, J. H., 79-5438
 Clarke, G. C., 79-5766
 Clayton, A. F., 79-5597
 Cleaver, J. E., 79-5993
 Clements, J. B., 79-5770
 Clynes, M. M., 79-5978
 Coca-Prados, M., 79-5802
 Cocos, M., 79-5637
 Codrington, J. F., 79-5847
 79-5848
 Coffin, J. M., 79-5721
 Coggin, J. H., 79-5836
 Cohen, E. P., 79-5831
 Cohen, I. K., 79-5636
 Cohr, K. H., 79-5418
 Coleman, C., 79-5935
 Coles, B. F., 79-5620
 Colman, A., 79-5976
 Colyer, S. P., 79-5540
 Compans, R. W., 79-5755
 Conney, A. H., 79-5634
 Cool, D. A., 79-5683
 Cool, W. S., 79-5683
 Coombs, M. M., 79-5597
 Cooper, A. G., 79-5847, 79-5848
 Cooper, G. M., 79-5708
 Copeland, N. G., 79-5708
 Copeland, T. D., 79-5763
 Corneci, I., 79-5639
 Costa Baptista, J. C., 79-5901
 Coulomb, B., 79-5983
 Coumaros, D., 79-5966
 Countryman, P. I., 79-5851
 Coupez, F., 79-5923
 Coustou, F., 79-5403
 Crathorn, A. R., 79-5567
 Cresteil, T., 79-5638
 Crittenden, L. B., 79-5720
 Croisy, A., 79-5526
 Cros, R. C., 79-5972
 Cruse, P., 79-5505
 Cserhati, G., 79-5899
 Csuka, O., 79-5519
 Cuddihy, R. G., 79-5684
 Cudkowicz, G., 79-5460, 79-5462
 79-5463
 Cutler, L. S., 79-5685
 Czeizel, E., 79-5499
 D'Amato, R., 79-5533
 Dahlberg, J. E., 79-5752
 Dalager, N. A., 79-5933
 Daly, J. J., 79-5539
 Dambaugh, T., 79-5779
 Danes, B. S., 79-5902
 Daneshmend, T. K., 79-5548
 Daniel, V., 79-5833
 Darai, G., 79-5777
 Darlix, J. L., 79-5717
 Darnell, J. E., 79-5811
 Dasgupta, A., 79-5822
 Davidson, H. G., 79-5919
 Davies, D. S., 79-5518
 Davies, R. E., 79-5446
 Davis, W., 79-5402, 79-5510
 Day, N. K., 79-5769

- Daynes, R. A., 79-5834
de Andrade, J. I., 79-5904
de Crombrughe, B., 79-5716
De Larco, J. E., 79-5622
de Meester, C., 79-5609
de Peyster, A., 79-5674
De Ren, G., 79-5973
De Ruiter, H. J., 79-5612
de Sousa, M., 79-5823
de-The, G., 79-5784
de Vitry, F., 79-5980
Declève, A., 79-5726
Dehnen, W., 79-5423
Delavierre, P., 79-5897
Delmont, J., 79-5842
Deobagkar, D. N., 79-5760
Desgranges, C., 79-5784
Devars Du Mayne, J. F., 79-5481
Devoret, R., 79-5424
Dew, M. J., 79-5912
Dexter, D. L., 79-5999
Dhiman, J., 79-5694
Dickson, C., 79-5730
Diegelmann, R. F., 79-5636
DiGiovanni, J., 79-5629
Dilley, J. V., 79-5682
Dillinger, P., 79-5485
Dimitrov, D. H., 79-5767
Dion, A. S., 79-5458
DiPaolo, J. A., 79-5640
Diwok, K., 79-5975
Doctor, G., 79-5661
Doerfler, W., 79-5818
Doffoel, M., 79-5966
Doig, D., 79-5743
Doll, R., 79-5493, 79-5957
Doloy, M. T., 79-5645
Donahue, V., 79-5668
Dorangeon, P., 79-5917
Dreher, B., 79-5865
Dreizin, R. S., 79-5767
Dressler, M., 79-5430
Drettner, B., 79-5601
Drohan, W., 79-5733
Drum, D. E., 79-5452
Dubitchev, A. G., 79-5767
Dubreuil, C., 79-5971
Duclos, J. C., 79-5971
Ducournau, R., 79-5968
Due, C., 79-5764
Duesberg, P. H., 79-5740
Dufrain, R. J., 79-5540
Dumont, A., 79-5461
Dusseire, P., 79-5967
Dvorak, H. F., 79-5459
Dybing, E., 79-5551
Eadie, G. G., 79-5683
Easton, G. D., 79-5631
Ebbesen, P., 79-5764
Eckhardt, S., 79-5703
Edwards, G., 79-5413
Egami, N., 79-5561
Egilsson, V., 79-5514
Ehrich, J. H., 79-5913
Einck, K. H., 79-5805
Eisenbrand, G., 79-5546
Elder, J. B., 79-5415
Elek, G., 79-5702
Eliseev, V. V., 79-5677
ElJack, A. H., 79-5521, 79-5522
Elkins, W. L., 79-5460, 79-5462
Elovaara, E., 79-5523, 79-5602
Embleton, M. J., 79-5467
England, J. M., 79-5718
Engler, G., 79-5810
English, D. R., 79-5949
Enjoji, M., 79-5911
Enstrom, J. E., 79-5496
Epstein, S. S., 79-5553
Erflé, V., 79-5693
Erickson, K. L., 79-5839
Ernst, P., 79-5905
Essex, M., 79-5761
Estis, L. F., 79-5710
Eun, C. K., 79-5852
Eusebi, V., 79-5860
Evans, I. H., 79-5514
Evans, L. H., 79-5740
Fadei, L., 79-5639
Fahl, W. E., 79-5657
Faivre, J., 79-5967
Falk, L., 79-5768
Fan, K. J., 79-5937
Fan, T. Y., 79-5413
Fanta, H., 79-5477
Farashian, V. R., 79-5709
Farris, A., 79-5861
Fayemi, A. O., 79-5944
Fedorova, S. M., 79-5698
Feigelson, P., 79-5544
Feldman, M., 79-5829
Fernandez, P. A., 79-5834
Festenstein, H., 79-5460
Fialkow, P. J., 79-5859
Fiers, W., 79-5810
Filippini, L., 79-5443
Filizzolo, F., 79-5869
Fine, D., 79-5731
Fine, D. H., 79-5413
Fine, D. L., 79-5735, 79-5766
Fischer, H., 79-5806
Fischer, P., 79-5513
Fisher, P. B., 79-5624, 79-5815
Fisk, S. R., 79-5617
Flatz, S., 79-5913
Fliniois, J. P., 79-5638
Flint, S. J., 79-5814
Florensa, L., 79-5855
Flugel, R. M., 79-5777
Foa, C., 79-5879
Foco, A., 79-5898
Foecking, M. K., 79-5596
Fogh, H., 79-5991
Fogh, J., 79-5991
Fogh, J. M., 79-5991
Foldes, I., 79-5702, 79-5704
Forbes, P. D., 79-5446
Forsberg, J. G., 79-5670
Frank, K., 79-5778
Frank, K. W., 79-5920
Franks, C. R., 79-5865
Fraser, N. W., 79-5811
Fraumeni, J. F., 79-5933
79-5945
Freedman, V. H., 79-5469
French, F. S., 79-5979
Friedell, G. H., 79-5486
79-5910
Friedman, J. M., 79-5859
Fry, J. R., 79-5552
Fujii, K., 79-5553
Fujii, M., 79-5572
Fujinaga, K., 79-5816
Fujita, S., 79-5895
Fujiyama, N., 79-5914
Fukuda, H., 79-5890
Funes-Cravioto, F., 79-5605
Furuno, A., 79-5791
Furuya, T., 79-5572
Gaakeer, H. A., 79-5612
Gaber, V. K., 79-5711
Gallagher, R., 79-5764
Gallatin, W. M., 79-5724
Gallo, R. C., 79-5821
Galos, R. S., 79-5814
Gambacorta, M., 79-5869
Gambrell, R. D., 79-5439
Ganguli, P. C., 79-5415
Garbarini, A., 79-5898
Gardner, M. B., 79-5749
Garner, R. C., 79-5422, 79-5620
Gati, E., 79-5519
Gaunt, S. J., 79-5990
Gavel, M., 79-5922
Gaynor, A., 79-5692
Gazit, A., 79-5820
Gazzolo, L., 79-5812
Geacintov, N. E., 79-5659
Gehly, E. B., 79-5657
Gehring, P. J., 79-5527
Geier, A., 79-5637
Gelboin, H. V., 79-5660
Gelderblom, H., 79-5777
Gerasimenko, P. P., 79-5662
Gerlach, S. M., 79-5901
Gerstmann, K. E., 79-5943
Gest, J., 79-5969
Gierek, T., 79-5844
Gilden, R. V., 79-5763
Gill, W. B., 79-5671
Gillespie, I. E., 79-5415
Gingell, R., 79-5564
Ginzburg, R., 79-5637
Giovannella, B., 79-5783
Giovanni, M. Y., 79-5984
Girard, M., 79-5966
Gisser, S. D., 79-5893
Giuntoli, R. L., 79-5442
Given, D., 79-5779
Glaser, M., 79-5804
Gleason, G. L., 79-5633
Glick, M. C., 79-5984
Golan, A., 79-5954
Gold, E. B., 79-5938
Goldstein, J. L., 79-5988
Goldstein, N. I., 79-5815
Golub, E. S., 79-5462
Gomes de Oliveira, G., 79-5901
Gomez-Garcia, P., 79-5867
Gomez-Pereira, C., 79-5867
Gonzalez-Campora, R., 79-5919
Good, R. A., 79-5769
Goodman, D. G., 79-5538
Goodrich-Smith, M., 79-5997
Gordis, L., 79-5938
Goto, M., 79-5598
Grab, D. J., 79-5517
Grabel, L. B., 79-5989
Grabow, D., 79-5871
Gradinaru, M., 79-5453
Graham, C. F., 79-5990
Graham, S., 79-5952
Grandis, C., 79-5896
Gray, J. W., 79-5995
Green, D., 79-5686
Green, M., 79-5817
Green, S., 79-5583
Green, W. R., 79-5744
Greenblatt, R. B., 79-5439
Greene, M. H., 79-5933
Greenfield, R. S., 79-5803
Gresser, I., 79-5787
Griffin, A. C., 79-5405
Griffin, B., 79-5579
Griffin, B. E., 79-5786
Griffin, J. D., 79-5801
Grinchishin, V. P., 79-5562
Grodzicker, T., 79-5809
Groneberg, J., 79-5818
Groner, Y., 79-5795, 79-5796
Grubbs, C. J., 79-5643
Gudkov, A. V., 79-5709
Guinivan, P., 79-5748
Gupta, S., 79-5769
Gurley, W. B., 79-5981
Gurtoo, H. L., 79-5661
Guslandi, M., 79-5416
Gusovskaia, I. M., 79-5756
Gutmann, H. R., 79-5556
Gyapay, G., 79-5700
Haga, M., 79-5572
Hageman, P., 79-5734
Hagmar, B., 79-5641
Haguenauer, J. P., 79-5971
Hahn, B. S., 79-5581
Haigh, R., 79-5429
Haimsohn, M., 79-5637
Hakama, M., 79-5956
Halperin, D., 79-5820
Halpern, M. S., 79-5718
Hamilton, M. G., 79-5517
Hamilton, R. C., 79-5819
Hammar, S. P., 79-5991
Hanafusa, H., 79-5707
Hanania, N., 79-5798
Hanselmayer, H., 79-5877
Hara, H., 79-5908
Hardin, J. W., 79-5438
Hardisty, J. F., 79-5531
Hardouin, J. P., 79-5481
Hardy, M., 79-5645
Harel, J., 79-5798
Harewood, K., 79-5821
Hargraves, W. A., 79-5616
Harkonen, W. S., 79-5832
Harnden, D. G., 79-5444
Harris, R. M., 79-5753
Harrison, T., 79-5813
Hartley-Asp, B., 79-5587
Hartley, J. W., 79-5727
Hartman, P. E., 79-5557
Haug, L. T., 79-5551
Haugen, A., 79-5569
Hauser, W. A., 79-5938
Hautvast, J. G., 79-5506
Hayashi, S., 79-5665
Hayward, W. S., 79-5707
Hearne, E., 79-5853
Hecht, S. S., 79-5414
Heddlé, J. A., 79-5851
Heidelberg, C., 79-5657
Heine, H. S., 79-5604
Heintz, N., 79-5621
Hemminki, K., 79-5523
Henderson, J. F., 79-5977
Henderson, L. E., 79-5763
Henderson, P. T., 79-5580
Hennekens, C. H., 79-5950
Henney, C. S., 79-5460, 79-5744
Hennings, H., 79-5633
Heppner, G. H., 79-5999
Hermus, R. J., 79-5506
Herstoff, J. K., 79-5884
Hesse, J., 79-5764
Hewlett, J. S., 79-5866
Hietanen, E., 79-5532
Higgins, J., 79-5837
Hikichi, M., 79-5572
Hill, J. A., 79-5887
Hinman, F., 79-5487
Hirakawa, T., 79-5651
Hirayama, T., 79-5965
Hirono, I., 79-5572
Hite, M., 79-5545
Hites, R. A., 79-5650
Hiza, P. R., 79-5960
Hofer, H. O., 79-5854
Hoffmann, D., 79-5414
Holben, J. A., 79-5736
Hollenberg, N. K., 79-5994
Holmes, F. F., 79-5853
Holst, J. J., 79-5483
Holtz, J. L., 79-5935
Honda, K., 79-5963
Honma, Y., 79-5824
Honsik, C., 79-5829
Hoover, E. A., 79-5759
Horacek, J., 79-5690
Hosaka, S., 79-5572
Hoshino, T., 79-5995
Hosoda, Y., 79-5964
Howells, G. R., 79-5686
Howley, P. M., 79-5788
Hozier, J., 79-5827
Hozumi, M., 79-5824
Hruban, Z., 79-5489
Hrudka, F., 79-5521, 79-5522
Hsu, M. T., 79-5802
Hu, F., 79-5839, 79-5992
Hubel, K., 79-5877
Hucher, M., 79-5968, 79-5969
Huggins, G. R., 79-5442
Hughes, S., 79-5713
Hureau, J., 79-5897
Hurley, M. P., 79-5978
Ibba, F., 79-5898
Ida, K., 79-5504
Ihle, J. N., 79-5726
Iida, M., 79-5873

Ikawa, Y., 79-5739
 Imai, H., 79-5963
 Ingram, A. J., 79-5654
 Inui, N., 79-5610
 Irving, C. C., 79-5558
 Irwin, R. J., 79-5539
 Irzhanov, S. I., 79-5918
 Ishihara, A., 79-5906
 Ishii, T., 79-5964
 Ishikawa, T., 79-5560
 Ishizaki, Y., 79-5996
 Israel, E., 79-5825
 Ito, M., 79-5890
 Itoh, H., 79-5873
 Iudov, N. N., 79-5889
 Iwasaka, T., 79-5774
 Iwasaki, H., 79-5911
 Iwasaki, T., 79-5574
 Izumi, T., 79-5845
 Jacobs, A. H., 79-5480
 Jacobs, J. B., 79-5486
 Jacobson, R. J., 79-5859
 Jakasa, V., 79-5880
 Jalobceastii, L., 79-5876
 Jameela, 79-5611
 Janin, M. L., 79-5968, 79-5969
 Janowski, M., 79-5754
 Jasmin, C., 79-5456
 Jeanloz, R. W., 79-5848
 Jefcoate, C. R., 79-5657
 Jellinger, K., 79-5863
 Jeney, A., 79-5700
 Jensen, G., 79-5764
 Jerina, D. M., 79-5634
 Jick, H., 79-5940, 79-5948
 Johannessen, J. V., 79-5490
 Johansson-Brittebo, E., 79-5578
 Johnson, E. F., 79-5647
 Johnson, H. W., 79-5883
 Jones, A. H., 79-5629
 Jones, K., 79-5957
 Joosting, A. C., 79-5954
 Jordan, S. W., 79-5667
 Joseph, P. G., 79-5452
 Juchau, M. R., 79-5629
 Judah, D. J., 79-5618
 Justrabo, E., 79-5843
 Kaden, D. A., 79-5650
 Kado, M., 79-5845
 Kahana, C., 79-5795, 79-5796
 Kainer, R. A., 79-5475
 Kak, S. N., 79-5543
 Kalland, T., 79-5670
 Kamran, D., 79-5913
 Kandarkar, S. V., 79-5535
 Kang, K. Y., 79-5533
 Kann, J., 79-5546
 Kano, M., 79-5911
 Kapadia, A., 79-5769
 Kaplan, E., 79-5556
 Kaplan, H. S., 79-5726, 79-5829
 Karess, R. E., 79-5707
 Karjalainen, H. E., 79-5790
 Karran, P., 79-5579
 Karsenty, C., 79-5842
 Kasamatsu, H., 79-5807
 Kaschka-Dierich, C., 79-5722
 Kasukabe, T., 79-5824
 Kato, Y., 79-5841
 Kauffman, S. L., 79-5891
 Kaul, B. L., 79-5543, 79-5603
 Kautz, G., 79-5488
 Kawachi, T., 79-5591
 Kawahara, A. A., 79-5470
 Kawai, K., 79-5504
 Keller, L. H., 79-5719
 Kemp, J. D., 79-5981
 Kemp, M. C., 79-5755
 Kennaway, D. J., 79-5664
 Kensler, T. W., 79-5623
 Kent, D. R., 79-5503
 Keppling, C., 79-5967
 Kersey, J. H., 79-5827
 Kessous, A., 79-5773, 79-5775
 Khan, A. S., 79-5760
 Khar'kovskaia, N. A., 79-5673
 Khoury, G., 79-5789
 Khudolei, V. V., 79-5593
 Kieff, E., 79-5779
 Kilian, D. J., 79-5583
 Kim, B. S., 79-5830, 79-5831
 Kim, Y. S., 79-6000
 King, C. M., 79-5615
 King, L. J., 79-5552
 King, M. C., 79-5947
 King, W., 79-5779
 Kino, I., 79-5841
 Kinoshita, K., 79-5642
 Kirchhoffova, A., 79-5926
 Kirk, M. E., 79-5440
 Kirkwood, J. M., 79-5672
 Kirschenbaum, M. B., 79-5878
 Kissoneghis, A. M., 79-5597
 Kitaichi, M., 79-5845
 Kizaki, H., 79-5466
 Kjellstrand, C. M., 79-5500
 Klapwijk, P. M., 79-5576
 Klein, G., 79-5768, 79-5781
 79-5783
 Klein, R., 79-5546
 Kleinkauf, H., 79-5980
 Klessig, D. F., 79-5809
 Klinger, H. P., 79-5852
 Klotzer, W., 79-5594
 Knopf, K. W., 79-5771
 Knowlson, G. T., 79-5916
 Kobara, Y., 79-5963
 Kobayashi, H., 79-5725
 Koch, P., 79-5905
 Kock, E., 79-5928
 Koder, Y., 79-5991
 Koeppe, H. W., 79-5485
 Kohli, Y., 79-5504
 Kohn, K. W., 79-5542
 Kohn, D. E., 79-5750
 Koide, O., 79-5856
 Kolar, G. F., 79-5584
 Kolias, S. I., 79-5782
 Kolmodin-Hedman, B., 79-5605
 Komeiji, D. Y., 79-5515
 Koo, C., 79-5486
 Kornfeld, M., 79-5667
 Kornhuber, B., 79-5765
 Korobitsin, L. P., 79-5711
 Kosanovic, S., 79-5880
 Kosek, J. C., 79-5525
 Kostyal, A., 79-5900
 Koteen, G. M., 79-5649
 Kothbauer, P., 79-5863
 Kovalsky, I., 79-5700
 Kovi, J., 79-5937
 Krakowka, S., 79-5759
 Kramers, P. G., 79-5524
 Krepler, P., 79-5513
 Kress, C., 79-5787
 Krieger, M., 79-5988
 Krull, I. S., 79-5413
 Krupin, T., 79-5875
 Krzakowski, M., 79-5924
 Kubacki, S. J., 79-5411
 Kucerova, M., 79-5675
 Kudesia, M., 79-5838
 Kudrna, R. D., 79-5797
 Kunz, E., 79-5690
 Kunz, W., 79-5528
 Kuosma, E., 79-5956
 Kupfer, D., 79-5753
 Kurland, L. T., 79-5938
 Kurth, R., 79-5764
 Kushwaha, M. R., 79-5931
 Kuznetsov, O. K., 79-5698
 Kuzumaki, N., 79-5725
 Kyono, Y., 79-5561
 Labarthe, D. R., 79-5435
 Ladda, R. L., 79-5748
 Laerum, O. D., 79-5569
 Lagneau, A., 79-5843
 Lai, C. J., 79-5789
 Laib, R. J., 79-5528
 Lalitha, V. S., 79-5925
 Lamaze, R., 79-5973
 Lambert, S. I., 79-5933
 Lambert, B., 79-5586, 79-5605
 Lambotte-Vandepaer, M., 79-5609
 Lamy, P., 79-5973
 Landrigan, P. J., 79-5935
 Landthaler, M., 79-5881
 Langhans, P., 79-5488
 Lapis, K., 79-5490, 79-5700
 79-5701, 79-5702, 79-5703
 Laplante, L., 79-5846
 Lasfargues, E. Y., 79-5458
 Laskin, J. D., 79-5624
 Lasnitzki, I., 79-5644
 Lasser-Weiss, M., 79-5833
 Latarjet, R., 79-5445
 Lau, P. P., 79-5582
 Laube, H., 79-5765
 Lavi, S., 79-5796
 Lavoue, M. F., 79-5784
 Law, M. F., 79-5788
 Lawler, S. D., 79-5512
 Lawther, P. J., 79-5433
 Le Bouffant, L., 79-5892
 Le Go, R., 79-5645
 LeBien, T. W., 79-5827
 Leblond-Larouche, L., 79-5714
 LeBoeuf, R., 79-5661
 Lecomte, P., 79-5646
 Lecomte, P., 79-5923
 Lee, F., 79-5813
 Lee, I. P., 79-5577
 Lee, L. F., 79-5723
 Lee, S. A., 79-5821
 Lee, T. C., 79-5594
 Legator, M. S., 79-5583
 Legraverend, C., 79-5649
 79-5653
 Legresley, L. P., 79-5846
 Lehmann, F. G., 79-5959
 Lehr, R. E., 79-5634
 Lehtonen, M., 79-5956
 Leijdekkers, C. M., 79-5580
 Lemenager, J., 79-5892
 Lenz, W., 79-5870
 Lerner, A. B., 79-5672
 Leroux, J. P., 79-5638
 Lesca, P., 79-5646
 Lesko, S. A., 79-5656
 Levene, A. L., 79-5479
 Levey, G. S., 79-5590
 Levin, W., 79-5634
 Levis, A. G., 79-5537
 Levy, S., 79-5983
 Lewin, M., 79-5505
 Liang, W., 79-5831
 Liber, H. L., 79-5650
 Lieberman, M., 79-5726
 Lievaart, P. A., 79-5687
 Lijinsky, W., 79-5410, 79-5571
 Likhachev, A. J., 79-5584
 Lim, S., 79-5998
 Lindahl, T., 79-5579, 79-5768
 79-5780
 Lindblad, A., 79-5586
 Linder, M. C., 79-5998
 Lindsten, J., 79-5605
 Linial, M., 79-5715
 Linn, S., 79-5797
 Linsell, C. A., 79-5408
 79-5428
 Lippert, J., 79-5927
 Lisiewicz, J., 79-5844
 Littauer, U. Z., 79-5984
 Littlefield, L. G., 79-5540
 Liu, T. Z., 79-5406
 Livingston, D. M., 79-5801
 Long, C. A., 79-5458
 Long, C. W., 79-5747
 Long, F. X., 79-5888
 Longenecker, B. M., 79-5724
 Lopez-Revilla, R., 79-5559
 Lorentzen, R. J., 79-5656
 Lotjonen, S., 79-5614
 Loveless, J. D., 79-5991
 Lowing, R. K., 79-5552
 Luders, K., 79-5484
 Ludwig, G., 79-5628
 Lueker, D. C., 79-5475
 Luftiger, R. B., 79-5753
 Luh, Y., 79-5582
 Luka, J., 79-5781
 Lunenfeld, B., 79-5637
 Lunger, P. D., 79-5757
 Lupu, A., 79-5639
 Lurie, A. G., 79-5685
 Lutkeholter, G., 79-5975
 Luz, A., 79-5693
 Lynch, H. T., 79-5947
 Lyon, M., 79-5812
 MacGregor, A., 79-5819
 Mackey, J. K., 79-5817
 MacLeod, S. C., 79-5494
 Maeda, A., 79-5598
 Maeda, K., 79-5964
 Maeda, Y. Y., 79-5751
 Mahaffey, J. A., 79-5682
 Maheshwari, H. B., 79-5849
 Maisin, J. R., 79-5754
 Majkowski, J., 79-5924
 Majone, F., 79-5537
 Malagelada, J. R., 79-5501
 Malaveille, C., 79-5526
 Malik, G. B., 79-5838
 Maluf, W., 79-5904
 Manaker, R. A., 79-5789
 Mandard, J. C., 79-5892
 Mann, J. I., 79-5441
 Mansuy, D., 79-5646
 Mantyjari, R. A., 79-5790
 Marc, J., 79-5921
 Marciani, D. J., 79-5706
 Margison, G. P., 79-5584
 Marhuenda Sendra, F., 79-5953
 Maricic, Z., 79-5880
 Mark, R., 79-5547
 Markovits, P., 79-5983
 Marquart, K. H., 79-5693
 Marshall, R. R., 79-5680
 Martin, C. N., 79-5620
 Martin, F., 79-5843, 79-5967
 Martin, G. R., 79-5989
 Martin, G. S., 79-5713
 Martin, J. D., 79-5788
 Martin, M. S., 79-5843
 Martin, T. J., 79-5511
 Martinez-Guibelaide, F., 79-5867
 Marx, M. B., 79-5936
 Marx, P. A., 79-5742
 Mashiter, K., 79-5595
 Massey, R., 79-5731, 79-5735
 Mathes, L. E., 79-5759
 Matsubara, N., 79-5572
 Matsuda, Y., 79-5826
 Matsui, Y., 79-5845, 79-5963
 Matsukage, A., 79-5986
 Matsukura, N., 79-5591
 Matsumoto, H., 79-5515
 Matsuura, S., 79-5572
 Matter, A., 79-5644
 Matthews, C. D., 79-5664
 Matthews, R. H., 79-5596
 Mattison, D. R., 79-5658
 Mattocks, A. R., 79-5618
 Matz, B., 79-5777
 Maunoury, M. T., 79-5787
 Maunoury, R., 79-5983
 Maury, C., 79-5787
 May, E., 79-5798
 May, G., 79-5806
 Mays, E. T., 79-5941
 Mazze, R. I., 79-5525
 McCarter, J. A., 79-5728
 McCarthy, B., 79-5910
 McClellan, R. O., 79-5684
 McCloskey, J. A., 79-5554
 McCormack, S. A., 79-5438
 McCoy, G. D., 79-5414
 McCulloch, G., 79-5664

- McDonald, K., 79-5656
 McDonald, K. E., 79-5682
 McGuire, J. S., 79-5692
 McKee, R. H., 79-5599
 McKenzie, A. K., 79-5666
 McLoughlin, M. G., 79-5883
 McPartlin, M., 79-5597
 McPherson, K., 79-5957
 Medina Diez, J. M., 79-5953
 Mehrotra, R. M., 79-5931
 Meischke, H. R., 79-5762
 Menard, R. H., 79-5658
 Mendez, J. A., 79-5919
 Mendoza-Figueroa, T., 79-5559
 Meneguzzi, G., 79-5794
 Mennel, H. D., 79-5925
 Mercier, M., 79-5609
 Merino, F., 79-5835
 Merk, L. P., 79-5630
 Meruelo, D., 79-5455
 Messer, R. H., 79-5667
 Mey, U., 79-5464
 Meyers, J., 79-5640
 Michalides, R., 79-5734
 Michalova, K., 79-5573
 Michel, M. F., 79-5843
 Michelazzi, A., 79-5915
 Michiels, R., 79-5967
 Mihail, G., 79-5453
 Milanese, G., 79-5794
 Milgram, J. W., 79-5887
 Milgrom, F., 79-5835
 Milham, S., 79-5939
 Miller, D. K., 79-5847, 79-5848
 Miller, H. N., 79-5660
 Minh, H. N., 79-5923
 Minowada, J., 79-5827
 Minton, J. P., 79-5596
 Mintz, B., 79-5988
 Mirzaizants, G. G., 79-5662
 Misaki, F., 79-5504
 Mittal, M. M., 79-5849
 Miyagi, M., 79-5640
 Miyakawa, M., 79-5574
 Miyazono, J., 79-5774
 Mobini, J., 79-5547
 Moll, B., 79-5727
 Momeni, M. H., 79-5678
 Moncure, C. W., 79-5636
 Moohr, J. W., 79-5859
 Moon, R. C., 79-5643
 Moor, J. E., 79-5998
 Moore, C. W., 79-5613
 Moore, D. H., 79-5458, 79-5736
 Moore, M. A., 79-5455, 79-5463
 79-5741
 Morais, R., 79-5714
 Morard, J. L., 79-5921
 Moreland, F. M., 79-5583
 Mori, M., 79-5610
 Mori, R., 79-5774
 Moroni, P., 79-5860
 Morris, H. P., 79-5407
 Morrison, A. S., 79-5940
 Morser, J., 79-5976
 Morton, K. C., 79-5615
 Moshell, A. N., 79-5448
 Motoaki, O., 79-5845
 Mucke, H., 79-5975
 Mudryj, M., 79-5557
 Mueller, G. C., 79-5623
 Mufson, R. A., 79-5624
 Muhlenstedt, D., 79-5870
 Mukamel, A., 79-5795
 Mukerjee, P., 79-5849
 Mullen, P. W., 79-5416
 Muller-Eberhard, U., 79-5647
 Muller, H., 79-5474
 Muller-Salamin, L., 79-5644
 Muncunill, J., 79-5855
 Munk, K., 79-5777
 Munthe-Kaas, A. C., 79-5482
 Murphy, G. P., 79-5942
 Murphy, W. M., 79-5558
 Muschol, E., 79-5450
 Muscianese, V., 79-5882
 Mushkacheva, G. S., 79-5676
 Musilova, J., 79-5573
 Muto, T., 79-5791
 Muzyczka, N., 79-5799
 Nacheva, E., 79-5513
 Nadler, L. M., 79-5828
 Naeser, P., 79-5928
 Nagafuchi, S., 79-5774
 Nagar, R., 79-5849
 Nagasawa, H., 79-5665
 Nagel, D., 79-5564
 Nagel, G. A., 79-5854
 Nagel-Studer, E., 79-5854
 Nagpaul, K. K., 79-5694
 Nakadaira, A., 79-5901
 Nakamura, K., 79-5964
 Nakayama, M., 79-5572
 Namkung, M. J., 79-5629
 Naroditskii, B. S., 79-5709
 Naroditsky, B. S., 79-5767
 Natarajan, A. T., 79-5575
 Naves Junqueira, J. F., 79-5904
 Nazerian, K., 79-5722
 Neal, G. E., 79-5618
 Nehorayan, A., 79-5807
 Neiman, P. E., 79-5720
 Neishtadt, E. L., 79-5711
 Nemoto, N., 79-5651
 Newhouse, M. L., 79-5404
 Nieh, P. T., 79-5539
 Nilsson, K., 79-5783
 Nishi, Y., 79-5610
 Nishimura, M., 79-5536
 Nishiya, I., 79-5996
 Nishizuka, Y., 79-5732
 Nissen, E. D., 79-5503
 Nissen, S. E., 79-5503
 Noble, G. R., 79-5764
 Noel, G., 79-5609
 Nogales, F. F., 79-5919
 Nola, P., 79-5880
 Nomdedeu, B., 79-5855
 Nomura, K., 79-5995
 Nooter, K., 79-5821
 Norberg, E., 79-5605
 Nordenskjold, M., 79-5605
 Nordlund, J. J., 79-5672
 Norkin, L. C., 79-5805
 Norman, R. L., 79-5647
 Nowakowski, W., 79-5924
 Nowinski, R. C., 79-5744
 Nunez-Ollero, G., 79-5867
 Nunez-Roldan, A., 79-5867
 Nusse, R., 79-5734
 O'Connor, P. J., 79-5588
 O'Fallon, W. M., 79-5435
 Obukh, I. B., 79-5709
 Oda, H., 79-5774
 Ogasawara, M., 79-5986
 Ogier, G., 79-5812
 Ohsato, K., 79-5873
 Ohta, Y., 79-5841
 Ohtaki, K., 79-5681
 Okabe, J., 79-5824
 Okano, P., 79-5660
 Okazaki, W., 79-5720
 Olin, R., 79-5605
 Olive, P. L., 79-5585
 Oliveira Almeida, H., 79-5904
 Oliveri, M., 79-5896
 Olivero, S., 79-5898
 Olivieri, P., 79-5696
 Olsen, R. G., 79-5759
 Olson, J. W., 79-5563
 Ono, K., 79-5986
 Orchard, M. E., 79-5954
 Oroszlan, S., 79-5763
 Ortiz, V. N., 79-5691
 Oshima, S., 79-5845, 79-5963
 Osipova, L. A., 79-5562
 Osterkamp, U., 79-5566
 Ostertag, H., 79-5913
 Ott, H., 79-5429
 Owens, I. S., 79-5649, 79-5653
 Padykula, H. A., 79-5438
 Page, D. L., 79-5507
 Page, N. N., 79-5401
 Paglia, D., 79-5868
 Pak, K., 79-5574
 Pala, S., 79-5857
 Palmer, K. A., 79-5583
 Pan, M., 79-5692
 Panicker, K. N., 79-5886
 Paoletti, C., 79-5646
 Papamatheakis, J. D., 79-5706
 Papas, T. S., 79-5705
 Paradisi, M., 79-5882
 Park, C. N., 79-5527
 Parker, N. B., 79-5661
 Parkman, R., 79-5455
 Pastan, I., 79-5716
 Patel, J. M., 79-5607
 Patet, J., 79-5784
 Pauli, B. U., 79-5486
 Paulson, D. F., 79-5420
 Pavlovic, A., 79-5517
 Pawlicki, M., 79-5930
 Peck, H., 79-5545
 Pedersen, N. C., 79-5837
 Pelkonen, K., 79-5532
 Pelkonen, O., 79-5653, 79-5655
 Penhoet, E. E., 79-5797
 Perdomo, J., 79-6000
 Perrin, C., 79-5888
 Peter, S., 79-5499
 Peters, G., 79-5752
 Peterson, W. A., 79-5935
 Petiet, G., 79-5973
 Peto, R., 79-5950
 Pfister, A., 79-5638
 Philpot, R. M., 79-5607
 Pilch, J., 79-5844
 Pizer, L., 79-5772
 Placek, V., 79-5690
 Plaetse, F. V., 79-5754
 Planche, G., 79-5526
 Plapinger, L., 79-5669
 Pliss, G. B., 79-5593
 Pohl-Ruling, J., 79-5513
 Polan, A., 79-5932
 Polatti, F., 79-5850
 Polikova, Z., 79-5675
 Poncellet, F., 79-5609
 Pontilena, N., 79-5872
 Popovic, S., 79-5880
 Popper, H., 79-5502
 Porter, J., 79-5940
 Porzig, K. J., 79-5758
 Potdar, G. G., 79-5886
 Pour, P., 79-5564
 Powell, A. T., 79-5779
 Poyot, G., 79-5970
 Prajda, N., 79-5703
 Pratilas, V., 79-5534
 Preston, C. M., 79-5770
 Pretell, J., 79-5803
 Preussmann, R., 79-5546
 Prieur, J., 79-5842
 Pritchett, R., 79-5779
 Prout, G. R., 79-5539
 Prusik, T., 79-5659
 Pruszczyński, M., 79-5476
 Pueyo, C., 79-5606
 Purlito, D. T., 79-5910
 Pye, D., 79-5819
 Pyysalo, H., 79-5614
 Quereux, C., 79-5917
 Quintrell, N., 79-5713
 Raab-Traub, N., 79-5779
 Radke, K., 79-5713
 Radomsky, J., 79-5484
 Radvanyi, G., 79-5900
 Ramirez Ramos, A., 79-5504
 Rampal, P., 79-5842
 Rankow, R. M., 79-5872
 Raposa, T., 79-5575
 Rasheed, S., 79-5749
 Ratovitskii, E. A., 79-5711
 Redpath, J. L., 79-5688
 Rees, I., 79-5534
 Reid, L. C., 79-5472
 Reillaudou, M., 79-5645
 Reinherz, E. L., 79-5828
 Reith, A., 79-5627
 Reitz, M. S., 79-5745, 79-5821
 Repman, M. A., 79-5475
 Reske-Kunz, A. B., 79-5823
 Reuber, M. D., 79-5417, 79-5434
 Revina, V. S., 79-5676
 Reynolds, F. H., 79-5760
 Reynolds, R. K., 79-5760
 Reznik, G., 79-5531
 Rhim, J. S., 79-5746
 Rhoads, J. E., 79-5547
 Ribeiro de Melo, N., 79-5901
 Rice, J. M., 79-5550
 Rice, S. A., 79-5525
 Richardson, G. S., 79-5478
 Riessbeck, K. H., 79-5632
 Rigden, P., 79-5817
 Rinehart, W., 79-5545
 Ringborg, U., 79-5586
 Robb, J. A., 79-5792
 Robbins, J. H., 79-5448
 Robbins, K. C., 79-5758
 Roberfroid, M., 79-5609
 Robert-Guroff, M., 79-5821
 Robins, P., 79-5589
 Robinson, H. L., 79-5699
 Robinson, R. C., 79-5660
 Rochette-Egly, C., 79-5625
 Rogers, L. W., 79-5507
 Roggero, F., 79-5896
 Rojas, F. A., 79-5895
 Rojko, J. L., 79-5759
 Roka, R., 79-5909
 Rokutanda, M., 79-5751
 Roller, P. P., 79-5550
 Rose, H., 79-5632
 Rosen, S., 79-5668
 Rosen, S. D., 79-5989
 Rosenberg, N., 79-5737
 Rosenfeld, C., 79-5402, 79-5510
 Rosner, B., 79-5950
 Rothman, K. J., 79-5940
 Rowe, W. P., 79-5727
 Rowley, R. D., 79-5792
 Rozenbaum, H., 79-5509
 Rozman, C., 79-5855
 Rua, S., 79-5696
 Rubic, I., 79-5907
 Ruddle, F. H., 79-5852
 Ruffi, T., 79-5864
 Rufner, R., 79-5719
 Runge, R., 79-5564
 Ruoslahti, E., 79-5465
 Russell, D. H., 79-5563
 Russfield, A., 79-5531
 Ryd, W., 79-5641
 Rymo, L., 79-5780
 Rytomaa, T., 79-5679
 Saab, G. A., 79-5862
 Saada, K., 79-5966
 Sacks, T. L., 79-5760
 Saffhill, R., 79-5588
 Saffiotti, U., 79-5432
 Sakagami, Y., 79-5732
 Sakakura, T., 79-5732
 Salk, J., 79-5454
 Sallan, S. E., 79-5828
 Salmasi, S., 79-5564
 Salmi, A., 79-5790
 Salnikow, J., 79-5980
 Salvaggio, J., 79-5533
 Samuel, K. P., 79-5705
 Sanders, C. L., 79-5682
 Sandmeyer, S., 79-5712
 Sanfelici, G., 79-5898
 Sanford, B. H., 79-5463
 Sano, T., 79-5591
 Santi, L., 79-5565
 Saracci, R., 79-5497
 Sargent, M. D., 79-5687
 Sarles, H., 79-5972

- Sasajima, K., 79-5591
 Sass, L., 79-5891
 Sassen, A., 79-5754
 Sato, A., 79-5963
 Saurel, J., 79-5921
 Savage, R. A., 79-5866
 Saxholm, H. J., 79-5627
 Sayer, A. M., 79-5540
 Schaeffer, W. I., 79-5621
 Scheid, M. P., 79-5823
 Schengrund, C. L., 79-5475
 Schilperoort, R. A., 79-5576
 Schlake, W., 79-5488
 Schleue, E., 79-5975
 Schlom, J., 79-5733
 Schlossman, S. F., 79-5828
 Schmick, A., 79-5613
 Schmitt, E. J., 79-5985
 Schmitz-Feuerhake, I., 79-5450
 Schneider, H. P., 79-5870
 Schneider, R., 79-5966
 Schnitzer, T. J., 79-5738
 Schochetman, G., 79-5731
 79-5735
 Schoenberg, H. W., 79-5671
 Schonleben, K., 79-5488
 Schotz, W., 79-5952
 Schram, K. H., 79-5554
 Schramm, T., 79-5425
 Schroder, B., 79-5566
 Schroder, C. H., 79-5777
 Schteingart, D. E., 79-5666
 Schueler, R., 79-5538
 Schulte-Overberg, S., 79-5693
 Schumacher, G. F., 79-5671
 Schwartz, P., 79-5973
 Schweid, A. I., 79-5949
 Schwesinger, G., 79-5858
 79-5871
 Scolnick, E. M., 79-5740
 79-5749
 Scott, D., 79-5680
 Scott, G. L., 79-5548
 Scott, L. E., 79-5998
 Scribner, J. D., 79-5554
 79-5555, 79-5617
 Scribner, N. K., 79-5554
 79-5555, 79-5617
 Seamark, R. F., 79-5664
 Sebek, B. A., 79-5866
 Seglen, P. O., 79-5492
 Sehgal, P. B., 79-5811
 Sekikawa, K., 79-5816
 Selvin, S., 79-5947
 Sen, A., 79-5729
 Seppala, M., 79-5465
 Serentha, U., 79-5898
 Serov, S. F., 79-5918
 Sevc, J., 79-5690
 Sevoian, M., 79-5719
 Sgro, M., 79-5903
 Shannon, M. F., 79-5978
 Shaool, D., 79-5798
 Shapiro, I. M., 79-5781
 Shaposhnikov, I. D., 79-5711
 Sharkey, N. A., 79-5542
 Sharp, P. A., 79-5813
 Shearer, G. M., 79-5455
 Sheffield, J. B., 79-5458
 Sheffler, B. A., 79-5475
 Sheibani, K., 79-5866
 Sheridan, A. P., 79-5741
 Sherman, A. I., 79-5920
 Shields, A., 79-5737
 Shih, T. Y., 79-5749
 Shima, A., 79-5561
 Shimba, H., 79-5681
 Shin, S., 79-5469, 79-5472
 Shiotani, T., 79-5466
 Shklar, G., 79-5630
 Shmel'kova, V. I., 79-5698
 Shooter, K. V., 79-5567
 Shorokhova, V. B., 79-5676
 Shows, T. B., 79-5852
 Shoyab, M., 79-5622
 Sibrack, L., 79-5692
 Silber, C., 79-5848
 Silianovska, K., 79-5808
 Silvany, A. M., 79-5473
 Simard, R., 79-5773, 79-5775
 Simonova, I. A., 79-5889
 Sims, W. L., 79-5936
 Singer, B., 79-5568, 79-5993
 Singer, J. W., 79-5859
 Singer, P. R., 79-5875
 Sinha, Y. N., 79-5663
 Sirenko, O. A., 79-5593
 Sirsat, S. M., 79-5535, 79-5886
 Sklar, L. S., 79-5987
 Skopek, T. R., 79-5650
 Slaga, T. J., 79-5633
 Slaughter, L. J., 79-5407
 Slayter, H. S., 79-5848
 Smadja, A., 79-5923
 Smadja-Joffe, F., 79-5456
 Small, M., 79-5833
 Smith, B. R., 79-5652
 Smith, C. M., 79-5977
 Smith, D. L., 79-5554
 Smith, J., 79-5797
 Smith, J. R., 79-5620
 Smith, M. E., 79-5875
 Smith, M. F., 79-5776
 Smith, R. G., 79-5821
 Smolar, N., 79-5786
 Soderlund, E., 79-5551
 Soeda, E., 79-5786
 Sofuni, T., 79-5681
 Soini, I., 79-5956
 Sokolova, A. N., 79-5698
 Solanke, T. F., 79-5961
 Somfai-Relle, S., 79-5519
 79-5520
 Somogyi, A., 79-5427
 Sorg, C., 79-5991
 Spahr, P. F., 79-5717
 Spangler, G., 79-5801
 Sparrins, V. L., 79-5516
 Spector, D., 79-5772
 Speizer, F. E., 79-5950
 Spiegelhalter, B., 79-5546
 Sporny, S., 79-5476
 Sprent, J., 79-5460, 79-5462
 Springer, J. A., 79-5583
 Stanley, P. I., 79-5529
 Staquet, M. J., 79-5785
 Stavrou, D., 79-5566
 Steel, L. K., 79-5765
 Steeves, R. A., 79-5455
 Stehlin, J. S., 79-5783
 Steinhäusl, H., 79-5874
 Stenberg, R., 79-5772
 Stenkvist, B., 79-5601
 Stenstrand, K., 79-5679
 Stepan, K., 79-5564
 Stephenson, J. R., 79-5760
 79-5763
 Sterling, T. D., 79-5495
 Stewart, I. B., 79-5475
 Stiles, C. D., 79-5470
 Stockle, G., 79-5528
 Stokholm, J., 79-5418
 Storb, R., 79-5463
 Strand, O., 79-5670
 Strandberg, J. D., 79-5538
 Straus, F. H., 79-5671
 Strnad, B. C., 79-5776
 Sturdee, D. W., 79-5439
 Stutman, O., 79-5462, 79-5471
 Suba, Z., 79-5700, 79-5703
 Subramanian, K. N., 79-5793
 Subramanyam, S., 79-5611
 Sugar, H. S., 79-5920
 Sugar, J., 79-5519, 79-5520
 Sugimura, T., 79-5591
 Sugiura, K., 79-5598
 Suh, M., 79-5775
 Suk, W. A., 79-5747
 Sullivan, F. M., 79-5437
 Sunder-Plassmann, E., 79-5863
 Sutton, D. W., 79-5981
 Suzuki, H., 79-5914
 Svet-Moldavskii, G. Ia.
 79-5756
 Swan, S. H., 79-5951
 Swenson, A., 79-5605
 Szekely, D. R., 79-5949
 Szilagyi, J., 79-5899
 Szklo, M., 79-5938
 Szymanowski, R., 79-5895
 Takahama, S., 79-5751
 Takahashi, G., 79-5642
 Takanashi, H., 79-5572
 Takata, R. H., 79-5515
 Takayama, S., 79-5560, 79-5651
 Takeichi, N., 79-5725
 Takemoto, K. K., 79-5788
 Talalay, P., 79-5604
 Tamaoki, N., 79-5914
 Tambourin, P. E., 79-5456
 Tamburro, C. H., 79-5426
 Taniguchi, H., 79-5665
 Tavassoli, M., 79-5862
 Taylor, A. M., 79-5444
 Taylor, H. W., 79-5571
 Teichmann, B., 79-5425
 Teller, M. N., 79-5594
 Temin, H. M., 79-5710
 Tevethia, S. S., 79-5803
 Thakker, D. R., 79-5634
 Theilen, G. H., 79-5837
 Theologides, A., 79-5832
 Theuws, J. L., 79-5580
 Thielmann, H. W., 79-5628
 Thilly, W. G., 79-5650
 Thiviolet, J., 79-5785
 Thomas, G. H., 79-5993
 Thomas, H. F., 79-5557
 Thompson, H., 79-5912
 Thompson, H. J., 79-5643
 Thoms, S., 79-5920
 Thomssen, R., 79-5722
 Thorgerisson, S. S., 79-5551
 Tice, A. J., 79-5558
 Tikhonenko, T. I., 79-5767
 Tikhonenko, T. I., 79-5709
 Till, J. E., 79-5455
 Tixier-Vidal, A., 79-5980
 Tjalve, H., 79-5578
 Todaro, G. J., 79-5622, 79-5729
 Tolson, M. R., 79-5620
 Tomatis, L., 79-5526
 Tometsko, A. M., 79-5599
 Tonascia, J. A., 79-5938
 Torres-Gomez, A., 79-5867
 Toth, B., 79-5549
 Toth, K., 79-5519, 79-5520
 Toyama, K., 79-5914
 Trainor, C. D., 79-5745
 Treves, A. J., 79-5829
 Troxler, D. H., 79-5740
 Trubcheninova, L. P., 79-5756
 Ts'o, P. O., 79-5656
 Tsao, H. S., 79-5666
 Tschlis, P. N., 79-5721
 Tsuji, H., 79-5901
 Tsuruoka, N., 79-5982
 Tubbs, R. R., 79-5866
 Turdakova, V. A., 79-5676
 Tzeng, D., 79-5466
 U.S. Environmental Protection
 Agency
 79-5431
 Uchida, E., 79-5572
 Uchida, S., 79-5791
 Ueno, I., 79-5572
 Ueyama, Y., 79-5914
 Umeda, M., 79-5536
 Ungeheuer, E., 79-5484
 Urbach, F., 79-5446
 Urban, J., 79-5573
 Vahakangas, K., 79-5655
 Vaidya, A. B., 79-5458
 Vainio, H., 79-5523, 79-5602
 Valenzuela, R., 79-5866
 van Beelen, P., 79-5576
 Van Bekkum, D. W., 79-5463
 van Buul, P. P., 79-5575
 van Deemter, L., 79-5734
 Van Der Hoff, N. M., 79-5962
 van Doorn, R., 79-5580
 Van Roy, F., 79-5810
 Vana, J., 79-5942
 Varmus, H. E., 79-5713
 Varnes, M. E., 79-5592
 Vasilenko, B. Kh., 79-5468
 Vaught, J. B., 79-5661
 Vayre, P., 79-5897
 Vedel, J. P., 79-5842
 Vella Briffa, D., 79-5447
 Veres, R., 79-5958
 Versari, P., 79-5869
 Vesely, D. L., 79-5590
 Veskova, T. K., 79-5756
 Vessey, M. P., 79-5957
 Viac, J., 79-5785
 Vianna, N. J., 79-5932
 Viglione, G. C., 79-5898
 Villa-Trevino, S., 79-5559
 Vincent, J. P., 79-5481
 Vives-Corrons, J. L., 79-5855
 Vogel, H., 79-5689
 Voglino, A., 79-5882
 Voller, A., 79-5764
 Vorherr, H., 79-5508, 79-5667
 Vorherr, U. F., 79-5667
 Vottero, G., 79-5898
 Vucusa, C., 79-5696
 Wagenaas-Zegers, M. A., 79-5580
 Wahi, R., 79-5825
 Wahl, P., 79-5917
 Wainberg, M. A., 79-5825
 Wake, C. T., 79-5800
 Walden, P. A., 79-5512
 Walker, A. M., 79-5948
 Walker, C. H., 79-5529
 Wallcave, L., 79-5564
 Wang, S. Y., 79-5581
 Wang, Y. Y., 79-5674
 Ward, J. M., 79-5531, 79-5538
 Warin, A. P., 79-5447
 Warner, N. L., 79-5462, 79-5463
 Warren, W., 79-5567
 Watanabe, H., 79-5873
 Watanabe, P. G., 79-5527
 Watanabe, S., 79-5791
 Watanabe, Y., 79-5856
 Watson, R. J., 79-5770
 Wattenberg, L. W., 79-5516
 Watts, R. H., 79-5686
 Wayand, W., 79-5909
 Weber, G., 79-5466
 Webster, D. J., 79-5596
 Weeks, C. E., 79-5633
 Wegener, T., 79-5959
 Weinstein, I. B., 79-5624
 79-5815
 Weinstein, R. S., 79-5486
 Weiss, N. S., 79-5949
 Weiss, R., 79-5863
 Weissbuch, H., 79-5453
 Welch, J. P., 79-5946
 Wellmann, K. F., 79-5943
 Welsch, C. W., 79-5997
 Wendel, H., 79-5975
 Wendling, F., 79-5456
 Wenk, M. L., 79-5550
 Wertz, P. W., 79-5623
 West, D. M., 79-5658
 Westlake, G. E., 79-5529
 Wharton, R. S., 79-5525
 Wheeler, R. H., 79-5451
 Wheelock, E. F., 79-5742
 Whitaker, J. A., 79-5894
 Whitehead, J. S., 79-6000
 Wigzell, H., 79-5460
 Wilkie, D., 79-5514
 Williams, J., 79-5813, 79-5814
 Williams, J. C., 79-5466
 Wilson, E. M., 79-5979
 Wilson, J. H., 79-5800

Wilson, M., 79-5997
 Wishnok, J. S., 79-5412
 Wislocki, P. G., 79-5634
 Witorsch, R. J., 79-5636
 Witter, R. L., 79-5720
 Wold, W. S., 79-5817
 Wolf, C. R., 79-5607
 Wolf, M. H., 79-5413
 Wolnik, L., 79-5955
 Woodbury, M. C., 79-5666
 Woodward, J. G., 79-5834
 Wright, W. C., 79-5991
 Wyplotz, J., 79-5892
 Wyrobek, A. J., 79-5421
 Yakovenko, K. N., 79-5530

Yamagiwa, H., 79-5906
 Yamamoto, N., 79-5626
 Yamane, T., 79-5908
 Yamashita, K., 79-5908
 Yanai, R., 79-5665
 Yang, J. P., 79-5910
 Yang, S. K., 79-5631
 Yaniv, A., 79-5820
 Yao, T., 79-5873
 Yasuhira, K., 79-5642
 Yeates, D., 79-5957
 Yim, O., 79-5783
 Yokoyama, S., 79-5982
 Yoshida, K., 79-5816
 Yoshida, M., 79-5739

Yoshida, O., 79-5574
 Yoshikura, H., 79-5739
 Young, H. A., 79-5749
 Young, I., 79-5893
 Young, S. W., 79-5994
 Zabel, M., 79-5840
 Zabilansky, E., 79-5688
 Zagol'skaia, V. N., 79-5918
 Zang, K. D., 79-5806
 Zanker, K., 79-5566
 Zapata-Gayon, C., 79-5605
 Zara, C., 79-5850
 Zavarzin, A. A., 79-5889
 Zbinden, G., 79-5577
 Zech, L., 79-5783

Zedeck, M. S., 79-5517
 Zefirova, G. S., 79-5662
 Zelenetz, A. D., 79-5708
 Zhdanov, V. M., 79-5709
 Zimmerman, H. J., 79-5436
 Zimmermann, B., 79-5968
 Ziskind, M., 79-5533
 Zollinger, M., 79-5714
 Zolnay, B., 79-5900
 Zombor, G., 79-5977
 Zuchowska-Vogelgesang, B.
 79-5930
 Zuck, P., 79-5973
 Zuckerman, A. J., 79-5457
 zur Hausen, H., 79-5626

Subject Index

Abnormalities

- Ethane, 1,2-Dibromo-Spermatzoa, 79-5521
- Hepatosoma
 - Kidney, 79-5916
- Radiation, Ionizing
 - Mutagenic Activity, 79-5689
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Urogenital System, Rat, 79-5667
- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - Ames Test
 - Structure-Activity Relationship, 79-5617
 - DNA Repair
 - Mutagenic Activity, 79-5617
- Acetamide, *N*-(Acetyloxy)-*N*-(4-(2-phenylethenyl)phenyl)-Adenosine
 - Cytidine, 79-5554
 - Cytidine
 - Nucleoside Adducts, 79-5554
 - Guanosine
 - Nucleoside Adducts, 79-5554
 - Nucleic Acids
 - Alkylation Reactions, 79-5555
 - Nucleoside Adducts, 79-5555
 - Polynucleotides
 - Alkylation Reactions, 79-5555
- Acetamide, *N*-Fluoren-2-yl-
 - Alpha Fetoproteins
 - Hepatotoxicity, 79-5552
 - Ames Test
 - S9 Fraction, 79-5629
 - 5,6-Benzoflavone
 - Metabolism, Liver, 79-5551
 - Endonucleases
 - Ultraviolet Rays, 79-5628
 - Hepatosoma
 - Piperonyl Butoxide, 79-5553
 - Precancerous Conditions, Review, 79-5489
 - Phenol, *p*-Nitro-
 - Metabolism, Liver, 79-5551
- Acetamide, *N*-Fluoren-3-yl-
 - Microsomes, Liver
 - Metabolism, 79-5556
- Acetamide, *N*-Fluoren-2-yl-di-
 - Hepatosoma
 - Growth, Review, 79-5407
- Acetamide, *N*-(9-Hydroxyfluoren-3-yl)-
 - Microsomes, Liver
 - Metabolism, 79-5556
- Acetamide, *N*-(9-Oxofluoren-3-yl)-
 - Microsomes, Liver
 - NADH, NADPH Oxidoreductases, 79-5556
- Acetanilide, 4'-(*p*-Fluorophenyl)-
 - Hepatosoma
 - Growth, Review, 79-5407
- Acetanilide, 4'-Phenyl-
 - Hepatosoma
 - Piperonyl Butoxide, 79-5553
- Acetic Acid, (2,4-Dichlorophenoxy)-
 - Occupational Hazard
 - Herbicides, Review, 79-5413
- Acetic Acid, Methylnitrosaminomethyl Ester
 - Gastrointestinal Neoplasms
 - Administration Route, Rat, 79-5550
 - Lung Neoplasms
 - Adenocarcinoma, 79-5550
 - Mammary Neoplasms, Experimental
 - Adenofibroma, 79-5550
 - Nervous System Neoplasms
 - Neurilemmoma, 79-5550

- Acetic Acid, Methylnitrosaminomethyl Ester (cont'd)
 - Neurilemmoma
 - Administration Route, Rat, 79-5550
 - Sebaceous Gland Neoplasms
 - Zymbal Gland, 79-5550
- Acetohydroxamic Acid, *N*-4-Biphenyl-
 - Piperonyl Butoxide
 - Hepatocarcinogenicity, 79-5553
- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Ames Test
 - Mutagenic Metabolite, 79-5551
 - Piperonyl Butoxide
 - Hepatocarcinogenicity, 79-5553
- p*-Acetophenetidine
 - Kidney Neoplasms
 - Carcinoma, Transitional Cell, 79-5612
- Acetophenone, 2-Amino-
 - Adrenal Gland Neoplasms
 - Carcinogenic Activity, Hamster, 79-5673
 - Granulosa Cell Tumor, 79-5673
 - Bladder Neoplasms
 - Adenoma, 79-5673
 - Carcinoma, 79-5673
 - Lung Neoplasms
 - Carcinoma, Epidermoid, 79-5673
 - Ovarian Neoplasms
 - Granulosa Cell Tumor, 79-5673
 - Testicular Neoplasms
 - Disgerminoma, 79-5673
- Acetylcholinesterase
 - Neuroblastoma
 - Cells, Cultured, 79-5984
- Acetylglucosaminidase
 - Laryngeal Neoplasms
 - Lymphocytes, 79-5844
- Acid Phosphatase
 - Virus, SV40
 - Lysosomes, 79-5805
- Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 - L Cells
 - DNA Replication, 79-5585
- Actin
 - Cell Transformation, Neoplastic
 - Mouse, Nude, Review, 79-5469
 - Virus, Murine Sarcoma
 - Protein Kinase, 79-5729
- Adelphane
 - Antihypertensive Agents
 - Chromosome Aberrations, 79-5611
 - Chromosome Aberrations
 - Mitosis, 79-5611
- Adenine, 3-Methyl-
 - Urea, Methyl Nitroso-
 - DNA Repair, 79-5567
- Adenocarcinoma
 - Bone Neoplasms
 - Wood, 79-5971
 - Colonic Neoplasms
 - Glycoproteins, 79-6000
 - Esophageal Neoplasms
 - Epidemiology, Nigeria, 79-5961
 - Esophagitis, Peptic, 79-5897
 - Fucose
 - Membrane Proteins, 79-6000
 - Gastrointestinal Neoplasms
 - Epidemiology, France, 79-5967
 - Gynecologic Neoplasms
 - DNA, 79-5996
 - Epidemiology, 79-5953
 - Intestinal Neoplasms
 - Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester), 79-5516

- Adenocarcinoma (cont'd)
 - Morpholine, *N*-Nitroso-, 79-5593
- Kidney Neoplasms
 - Erythropoietin, 79-5914
 - 1-Propanol, 2,3-Dibromo-, Phosphate, 79-5531
- Kidney Transplantation
 - Case Report, 79-5846
- Lung Neoplasms
 - Acetic Acid, Methylnitrosaminomethyl Ester, 79-5550
 - Amylases, 79-5890
 - Cholanthrene, 3-Methyl-, 79-5642
 - Hydrazine, 4-Hydroxymethylphenyl-, 79-5549
 - Immunity, Cellular, 79-5845
 - Iron, 79-5892
 - Neoplasm Metastasis, 79-5914
 - Occupational Hazard, 79-5892
 - Smoking, 79-5963
 - Transplantation, Heterologous, 79-5914
- Mammary Neoplasms, Experimental
 - Epiglycanin, 79-5847
 - Epiglycanin, Isolation and Characterization, 79-5848
- Petroleum
 - Transplantation, Heterologous, 79-5832
- Polycythemia
 - Erythropoietin, 79-5914
 - Transplantation, Heterologous, 79-5914
- Rectal Neoplasms
 - Genetics, 79-5899
- Stomach Neoplasms
 - Guanidine, 1-Propyl-3-nitro-1-nitroso-, 79-5591
 - Hermans' Syndrome, 79-5842
- Wood
 - Occupational Hazard, 79-5971
- Adenofibroma
 - Breast Diseases
 - Theophylline, 79-5596
 - Breast Neoplasms
 - Contraceptives, Oral, 79-5440
 - Mammary Neoplasms, Experimental
 - Acetic Acid, Methylnitrosaminomethyl Ester, 79-5550
- Adenoma
 - Adrenal Gland Neoplasms
 - Cushing's Syndrome, 79-5666
 - Testosterone, 79-5666
 - Bladder Neoplasms
 - Acetophenone, 2-Amino-, 79-5673
 - Intestinal Neoplasms
 - Cell Transformation, Neoplastic, 79-5902
 - Genetics, 79-5902
 - Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester), 79-5516
 - Morpholine, *N*-Nitroso-, 79-5593
 - Polyps, 79-5906
 - Intestinal Polyps
 - Cell Transformation, Neoplastic, 79-5902
 - Kidney Neoplasms
 - 1-Propanol, 2,3-Dibromo-, Phosphate, 79-5531
 - Liver Neoplasms
 - Contraceptives, oral, 79-5441, 79-5443
 - Lung Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5553
 - Cholanthrene, 3-Methyl-, 79-5642
 - Hydrazine, 4-Hydroxymethylphenyl-, 79-5549
 - Ultrastructural Study, 79-5891
 - Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-nitroso-, 79-5571
 - Urea, 1-(2-Chloroethyl)-3,3-dimethyl-1-nitroso-, 79-5571

- Adenoma (cont'd)**
 Urea, Ethyl Nitroso-, 79-5891
 Urea, 1,3,3-Tris(2-chloroethyl)-1-nitroso-, 79-5571
- Parathyroid Neoplasms**
 Neoplastic Endocrine-Like Syndromes 79-5868
- Pituitary Neoplasms**
 Prolactin, 79-5595
 Somatotropin, 79-5595
- Prolactin**
 Theophylline, 79-5595
 Thyrotropin Releasing Hormone 79-5595
- Somatotropin**
 Ergocryptine, 2-Bromo-, 79-5595
 Theophylline, 79-5595
 Thyrotropin Releasing Hormone 79-5595
- Stomach Neoplasms**
 Guanidine, 1-Propyl-3-nitro-1-nitroso- 79-5591
- Adenoma, Eosinophilic**
 Pituitary Neoplasms
 Neurofibromatosis, 79-5869
- Adenomatosis, Familial Endocrine**
 Gastrointestinal Neoplasms
 Peptides, Review, 79-5483
 Pituitary Neoplasms
 Case Report, 79-5870
 Thyroid Neoplasms
 Case Report, 79-5870
- Adenosine**
 Acetamide, *N*-(Acetyloxy)-*N*-(4-(2-phenylethenyl)phenyl)-
 Cytidine, 79-5554
- Adenosine Cyclic 3',5' Monophosphate**
 Diethylamine, *N*-Nitroso-
 Protein Kinase, 79-5563
 12-*O*-Tetradecanoylphorbol-13-acetate
 Catecholamines, 79-5625
 Prostaglandins E, 79-5625
- Adenosine, *N*-Methyl-**
 Virus, SV40
 RNA, Messenger, 79-5796
 RNA, Viral, 79-5796
- Adenosine Triphosphatase**
 Liver Neoplasms
 Ethylene, Chloro-, 79-5528
- Adenosine Triphosphate**
 Glucose, 2-Deoxy-
 Erythrocytes, 79-5977
 Tubercidin
 Erythrocytes, 79-5977
 Virus, SV40
 RNA, Messenger, 79-5795
- Adrenal Cortex Hormones**
 Nervous System Neoplasms
 Vasculitis, 79-5863
- Adrenal Gland Neoplasms**
 Acetophenone, 2-Amino-
 Carcinogenic Activity, Hamster 79-5673
- Adenoma**
 Cushing's Syndrome, 79-5666
 Testosterone, 79-5666
- Endrin**
 Carcinogenic Potential, Review 79-5434
- Granulosa Cell Tumor**
 Acetophenone, 2-Amino-, 79-5673
- Hyperaldosteronism**
 Case Report, 79-5662
 Dexamethasone, 79-5662
- Adrenal Glands**
 Benz(a)anthracene, 7,12-Dimethyl-
 Tissue Distribution, Rat, 79-5635
- Adriamycin**
 Ames Test
 Urinary Metabolite, 79-5574
- Chromatids**
 Chromosome Aberrations, 79-5573
 Lymphocytes, 79-5573
- Guanidine, 1-Propyl-3-nitro-1-nitroso-**
 Guanyl Cyclase, 79-5590
- Hydrazine**
 Guanyl Cyclase, 79-5590
- Aflatoxin B1**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Carcinogenic Metabolite, 79-5618
 Benzenecarboxiperoxoic Acid, 3-Chloro-
 DNA Adducts, 79-5620
 7,8-Benzoflavone
 Ames Test, 79-5646
- Cell Division**
 Aryl Hydrocarbon Hydroxylases 79-5621
 Hepatocytes, Rat, 79-5621
- DNA Replication**
 Precancerous Conditions, 79-5619
- Ellipticine, 9-Hydroxy-**
 Ames Test, 79-5646
- Glutathione**
 DNA, Binding, 79-5618
- Hepatoma**
 Epidemiology, Review, 79-5490
 Growth, Review, 79-5407
- Hyperplasia**
 Parenchymal Cells, Liver, 79-5619
- Microsomes, Liver**
 Carcinogenic Metabolite, 79-5618
- Necrosis**
 Parenchymal Cells, Liver, 79-5619
- RNA, Ribosomal**
 Nucleic Acids, Binding, 79-5620
- Aflatoxin B1, 9,10-Dihydro-9-(7-guanyl)-**
 10-hydroxy-
 Benzenecarboxiperoxoic Acid, 3-Chloro-
 DNA Adducts, 79-5620
- Aflatoxin G1**
 Benzenecarboxiperoxoic Acid, 3-Chloro-
 DNA Adducts, 79-5620
 RNA, Ribosomal
 Nucleic Acids, Binding, 79-5620
- Aging**
 Melanocytes
 Cell Division, 79-5992
 Diphenol Oxidases, 79-5992
- Agrobacterium tumefaciens**
 Extrachromosomal Inheritance
 Recombination Defective Mutants 79-5576
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Recombination Defective Mutants 79-5576
 Methanesulfonic Acid, Methyl Ester
 Transformation, Genetic, 79-5576
- Plant Tumors**
 DNA-RNA Hybridization, 79-5981
 Extrachromosomal Inheritance 79-5981
- Ultraviolet Rays**
 Transformation, Genetic, 79-5576
- Air Pollution**
 Carcinogen, Chemical
 Risk Evaluation, Review, 79-5510
- Alanine**
 Glioma
 Peptide Synthesis, 79-5980
- Alanine, 3-(3,4-Dihydroxyphenyl)-**
 Papilloma
 Nucleotides, Cyclic, 79-5632
- Alanine, 2-Methyl-**
 12-*O*-Tetradecanoylphorbol-13-acetate
 Metabolism, Lymphocytes, 79-5623
- Alcohol Oxidoreductases**
 Methanol, (Methyl-*ONN*-azoxy)-,
 Acetate (Ester)
 Phenol, (1,1-Dimethylethyl)-4-
 methoxy-, 79-5516
- Alcoholic Beverages**
 Pancreatitis
 Epidemiology, 79-5972
- Alkaline Phosphatase**
 Laryngeal Neoplasms
 Neutrophils, 79-5844
- ALP-15**
see Ethacryl
- Alpha Fetoproteins**
 Acetamide, *N*-Fluoren-2-yl-
 Hepatotoxicity, 79-5552
 Antibody Specificity
 Immunochemical Properties, Review 79-5465
 Cholanthrene, 3-Methyl-
 Hepatotoxicity, 79-5552
 6-Chrysenamine
 Hepatotoxicity, 79-5552
- Hepatoma**
 Carcinogen, Chemical, 79-5467
 Liver Cirrhosis, 79-5959
- Liver Neoplasms**
 Diagnosis and Prognosis, Review, 79-5465
- Neural Tube Defects**
 Fetal Pathology, Review, 79-5465
- Teratoid Tumor**
 Diagnosis and Prognosis, Review, 79-5465
- Alpha Globulins**
 Cycloheximide
 Liver, Rat, 79-5544
 RNA, Messenger, 79-5544
- Aluminum**
 Brain Neoplasms
 Occupational Hazard, 79-5939
- Lung Neoplasms**
 Occupational Hazard, 79-5939
- Lymphoma**
 Occupational Hazard, 79-5939
- Pancreatic Neoplasms**
 Occupational Hazard, 79-5939
- Amaranth**
 Food Additives
 Carcinogenic Potential, Review 79-5402
- Ames Test**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Structure-Activity Relationship 79-5617
 Acetamide, *N*-Fluoren-2-yl-
 S9 Fraction, 79-5629
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Mutagenic Metabolite, 79-5551
- Aflatoxin B1**
 7,8-Benzoflavone, 79-5646
 Ellipticine, 9-Hydroxy-, 79-5646
- 2-Anthracenamide**
 Mutagenic Metabolite, 79-5647
- Benz(a)anthracene, 7,12-Dimethyl-**
 S9 Fraction, 79-5629
- Benzene, (Epoxethyl)-**
 Microsomes, Liver, 79-5608
- Benztidine, *N*-Hydroxy-*N,N'*-diacetyl-**
 Mutagenic Metabolite, 79-5615
- Benzo(a)pyren-1-ol**
 7,8-Benzoflavone, 79-5649
 Mutagenic Activity, 79-5649
- Benzo(a)pyren-3-ol**
 Mutagenic Activity, 79-5649
- Benzo(a)pyren-9-ol**
 Mutagenic Activity, 79-5649
- Benzo(a)pyrene**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 79-5609
 Benzene, Ethyl-, 79-5609
 7,8-Benzoflavone, 79-5646
 Ellipticine, 9-Hydroxy-, 79-5646

Ames Test (cont'd)

- Mutagenic Metabolite, 79-5647
- S9 Fraction, 79-5629
- Styrene, 79-5609
- Biphenylidol, 4-Amino-
Structure-Activity Relationship
79-5617
- 1-Butanone, 4-(Methylnitrosamino)-1-(3-pyridyl)-
Hydroxy Derivatives, Review, 79-5414
- Carcinogen, Chemical
Mutation, Review, 79-5424
Review, 79-5423
- Cholanthrene, 3-Methyl-
7,8-Benzoflavone, 79-5646
- Ellipticine, 9-Hydroxy-, 79-5646
- p*-Cresol, 2,6-Di-*tert*-butyl-
Mutagens, 79-5599
- Ellipticine
Mutagens, 79-5646
- Ellipticine, 9-Fluoro-
Mutagens, 79-5646
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
Mutagenic Metabolite, 79-5526
- Ethanol, 1,1-Bis(*p*-chlorophenyl)-2,2,2-trichloro-
Mutagenic Metabolite, 79-5526
- Ethidium Bromide
7,8-Benzoflavone, 79-5646
- Ellipticine, 9-Hydroxy-, 79-5646
- Gossypol
Contraceptives, Male, 79-5674
- Hydroxylamine, *N*-Fluorenyl-2-yl-
Mutagenic Metabolite, 79-5551
- Methanol, (Methyl-*ONN*-azoxy)-
Glucuronic Acid Conjugate, 79-5515
- 2-Naphthylamine
Mutagenic Activity, 79-5617
- Nicotine, 1'-Demethyl-1'-nitroso-
Hydroxy Derivatives, Review, 79-5414
- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Mutagens, 79-5599
- Platinum, Diamminedichloro-, *cis*-
Mutagenic Activity, 79-5541
- Pyrrolidine, 1-Nitroso-
Hydroxy Derivatives, Review, 79-5414
- Smoking
Urine, 79-5580
- Sodium Azide
Carcinogenic Potential, Review
79-5406
- Styrene
Maleic Acid, Diethyl Ester, 79-5608
- Propane, 1,2-Epoxy-3,3,3-trichloro-
79-5608
- Thymine, 5,6-Dihydro-6-hydroperoxy-5-hydroxy-
Mutagenic Activity, 79-5581
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-
Mutagenic Activity, 79-5606
- Uracil, 5-Hydroperoxymethyl-
Mutagenic Activity, 79-5581

Amino Acids

- Virus, Bovine Leukemia
- Viral Proteins, 79-5763

Amylases

- Lung Neoplasms
- Adenocarcinoma, 79-5890
- Immunohistochemical Study, 79-5890

Amyloidosis

- Apudoma
Diagnosis, Review, 79-5481
- Hodgkin's Disease
Immune Response, Review, 79-5481
- Leukemia, Lymphocytic
Immune Response, Review, 79-5481
- Neoplastic Endocrine-Like Syndromes
Diagnosis, Review, 79-5481

Androgens

- Peptide Hydrolases
- Receptors, Hormone, 79-5979
- Phosphorofluoridic Acid, Bis(1-methylethyl) Ester

Androgens (cont'd)

- Receptors, Hormone, 79-5979
- Prostatic Neoplasms
- Receptors, Hormone, 79-5979
- Receptors, Hormone
- Prostate, Testis, Rat, 79-5979

Anemia, Aplastic

- Radiation, Ionizing
- Chromosome Aberrations, 79-5851

Anemia, Hemolytic

- Virus, Murine Leukemia
- Immunization, 79-5725

Anemia, Pernicious

- Neoplasms
- Epidemiology, 79-5853

Angioma

- Angiosarcoma
- Hydrazine, 4-Hydroxymethylphenyl-
79-5549
- Liver Neoplasms
- Hydrazine, 4-Hydroxymethylphenyl-
79-5549

Angiosarcoma

- Angioma
- Hydrazine, 4-Hydroxymethylphenyl-
79-5549
- Ethylene, Chloro-
Dose-Response Study, Rat, 79-5527
- Epidemiology, Review, 79-5436
- Mathematical Model, 79-5527
- Transplacental Carcinogenesis, Review
79-5437
- Geographic Factors
- Epidemiology, Review, 79-5502
- Hydrazine, Phenethyl-
Case Report, 79-5548
- Hyperplasia
- Precancerous Conditions, Review
79-5491
- Phosphoric Acid, 2-Chloro-1-(2,4,5-trichlorophenyl)vinyl Dimethyl
Histological Study, Mouse, 79-5538
- Senkirkine
- Carcinogenic Activity, Rat, 79-5572
- Thorium Dioxide
- Epidemiology, Review, 79-5436

Aniline, 2,4,6-Trimethyl-

- Hepatoma
- Growth, Review, 79-5407

Anorexia

- Pancreatic Neoplasms
- Diagnosis, Review, 79-5468

2-Anthracenamide

- Ames Test
- Mutagenic Metabolite, 79-5647
- Cytochrome P-450
- Mutagenic Metabolite, 79-5647

Anti-Antibodies

- Virus, Friend Murine Leukemia
- Immune Response, 79-5743
- Virus, Polyoma
- Interferon, 79-5787

Antibodies

- Virus, Feline Sarcoma
- Lymph Nodes, 79-5837

Antibodies, Viral

- Hodgkin's Disease
- Virus, Epstein-Barr, 79-5764
- Virus, Influenza, 79-5764
- Virus, Simian Sarcoma, 79-5764

Antibody Specificity

- Sarcoma
- Antigenic Determinants, 79-5835
- Cholanthrene, 3-Methyl-, 79-5835
- Virus, Friend Murine Leukemia
- Glycoproteins, 79-5742
- Virus, Gibbon Ape Lymphoma
- Reverse Transcriptase, 79-5765

Antibody Specificity (cont'd)

- Virus, Simian Sarcoma
- Reverse Transcriptase, 79-5765

Antigen-Antibody Reactions

- Lymphoma
- Cholanthrene, 3-Methyl-, 79-5835
- Mammary Neoplasms, Experimental
- Virus, Murine Mammary Tumor
79-5731
- Virus, Avian Reticuloendotheliosis
- B-Lymphocytes, 79-5719
- Virus, Feline Leukemia
- Prednisolone, Methyl-, 79-5759
- Virus, Murine Mammary Tumor
- Glycoproteins, 79-5731

Antigenic Determinants

- Cervix Neoplasms
- Isolation and Characterization
79-5776
- Virus, Herpes Simplex 2, 79-5776
- Lymphoma
- Virus, Gibbon Ape Lymphoma
79-5821
- Virus, Simian Sarcoma, 79-5821
- Sarcoma
- Antibody Specificity, 79-5835
- Virus, Abelson Murine Leukemia
- Cell Transformation, Neoplastic
79-5760
- Virus, Avian Leukosis
- Lymphocyte Transformation, 79-5825
- Virus, Rous Sarcoma, 79-5702
- Virus, Avian Myeloblastosis
- Lymphocyte Transformation, 79-5825
- Virus, Bovine Leukemia
- Virus, Feline Leukemia, 79-5763
- Virus, Feline Sarcoma
- Cell Transformation, Neoplastic
79-5760
- Virus, Friend Spleen Focus-Forming
- Virus, Rauscher Murine Leukemia
79-5739
- Virus, Harvey Murine Sarcoma
- Phosphoproteins, 79-5749
- Virus, Kirsten Murine Sarcoma
- Phosphoproteins, 79-5749
- Virus, Mink Cell Focus-Inducing
- Cell Transformation, Neoplastic
79-5760
- Virus, Murine Mammary Tumor
- Antigens, Viral, 79-5735
- Virus, Radiation Leukemia
- Virus, Rauscher Murine Leukemia
79-5754
- Virus, Rat Sarcoma
- Phosphoproteins, 79-5749
- Virus, Rauscher Murine Leukemia
- Virus, Sindbis, 79-5755
- Virus, Rous Sarcoma
- Lymphocyte Transformation, 79-5825

Antigens

- Hepatoma
- Cell Membrane, Review, 79-5467
- Leukemia, Myelocytic
- Blast Crisis, 79-5827
- Melanoma
- Hybrid Cells, 79-5839
- Virus, Friend Murine Leukemia
- Cell Membrane, 79-5743

Antigens, Neoplasm

- Breast Neoplasms
- Lymph Nodes, 79-5849
- Fibrosarcoma
- T-Lymphocytes, 79-5834
- Leukemia, Myelocytic
- Cell Differentiation, 79-5824
- Meningioma
- Virus, SV40, 79-5806
- Sarcoma
- Virus, Adeno 2, 79-5808
- Virus, Adeno 12, 79-5808
- Virus, Polyoma
- DNA, Viral, 79-5786
- Virus, SV40

- Antigens, Neoplasm (cont'd)**
 Concanavalin A, 79-5804
 DNA, Viral, 79-5792
 Phosphoproteins, 79-5801
 Protein Kinase, 79-5801
- Antigens, Viral**
 Burkitt's Lymphoma
 Virus, Epstein-Barr, 79-5781
 Leukemia
 Radiation, Ionizing, 79-5754
 Virus, Radiation Leukemia, 79-5754
 Virus, Rauscher Murine Leukemia
 79-5754
 Mammary Neoplasms, Experimental
 Virus, Murine Leukemia, 79-5735
 Virus, Murine Mammary Tumor
 79-5735
 Virus, AKR Murine Leukemia
 Immunity, Cellular, 79-5744
 Virus, Avian Leukosis
 Crosses, Genetic, 79-5699
 Virus, Epstein-Barr
 Lymphocyte Transformation, 79-5784
 Virus, Feline Leukemia
 Histocompatibility Antigens, 79-5761
 Virus, Gross Murine Leukemia
 Immunity, Cellular, 79-5744
 Virus, Murine Leukemia
 Transplantation Immunology, 79-5725
 Virus, Murine Mammary Tumor
 Antigenic Determinants, 79-5735
 Cell Membrane, 79-5735
 Immune Response, Review, 79-5458
 Virus, Rous-Associated
 Bursa of Fabricius, 79-5718
 Chick Embryo, 79-5718
 Virus, SV40
 Intracellular Distribution, 79-5807
 Temperature Sensitive Mutants
 79-5807
- Antihypertensive Agents**
 Adelphane
 Chromosome Aberrations, 79-5611
- Antilymphocyte Serum**
 Colonic Neoplasms
 T-Lymphocytes, 79-5547
 Mouth Neoplasms
 Transplantation, Homologous, 79-5630
 Virus, Marek's Disease Herpes
 B-Lymphocytes, 79-5723
 T-Lymphocytes, 79-5723
- Antineoplastic Agents**
 Colonic Neoplasms
 Clone Cells, 79-5999
 Guanyl Cyclase
 Uraclil, 5-(Bis(2-chloroethyl)amino)-
 79-5590
 Mammary Neoplasms, Experimental
 Clone Cells, 79-5999
- Antinuclear Factors**
 Melanoma
 Lupus Erythematosus, Discoid
 79-5884
- Antipyrine, 4-(Dimethylamino)-**
 Ascorbic Acid
 Nitrosation, 79-5546
 Dimethylamine, *N*-Nitroso-
 Drug Contamination, 79-5546
 Nitrogen Dioxide
 Nitrosation, 79-5546
- Apudoma**
 Amyloidosis
 Diagnosis, Review, 79-5481
- Apurinic Endonuclease**
 DNA
 Enzymatic Activity, 79-5628
- Arsenic**
 Lung Neoplasms
 Epidemiology, Review, 79-5498
 Skin Neoplasms
 Carcinoma, Basal Cell, 79-5534
- Arsenic (cont'd)**
 Tracheal Neoplasms
 Carcinoma, Epidermoid, 79-5534
- Aryl Hydrocarbon Hydroxylases**
 Aflatoxin B1
 Cell Division, 79-5621
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Microsomes, 79-5532
 Benz(a)anthracene
 Cytochrome P-450, 79-5657
 Microsomes, 79-5657
 Benz(a)anthracene, 7,12-Dimethyl-
 Cytochrome P-450, 79-5657
 Microsomes, 79-5657
 Benzo(a)pyrene
 Cell Division, 79-5621
 Cell Transformation, Neoplastic
 79-5657
 DNA, Binding, 79-5648
 Ovary, Mouse, 79-5658
 Cholanthrene, 3-Methyl-
 Hepatocytes, Rat, 79-5621
 Microsomes, 79-5532
 Microsomes, Liver, 79-5609
p-Cresol, 2,6-Di-*tert*-butyl-
 Microsomes, Liver, 79-5600
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 Microsomes, Liver, 79-5519
 Ethanol, 2-(2,4,5-Trichlorophenoxy)-
 Microsomes, Liver, 79-5519
 Ethyl Alcohol
 Microsomes, Liver, 79-5518
 Smoking
 Microsomes, Liver, 79-5518
 Styrene
 Microsomes, Liver, 79-5609
- Asbestos**
 Drug Packaging
 Carcinogenic Potential, Review
 79-5403
 Environmental Hazard
 Epidemiology, Review, 79-5433
 Hydrolases
 Macrophages, 79-5533
 Lung Neoplasms
 Epidemiology, Review, 79-5404
 Mesothelioma
 Epidemiology, Review, 79-5404
 Pleural Neoplasms
 Mesothelioma, 79-5974
- Asbestosis**
 Bronchial Neoplasms
 Carcinoma, 79-5975
 Lung Neoplasms
 Precancerous Conditions, Review
 79-5404
 Occupational Hazard
 Epidemiology, 79-5975
 Pleural Neoplasms
 Mesothelioma, 79-5975
- Ascorbic Acid**
 Antipyrine, 4-(Dimethylamino)-
 Nitrosation, 79-5546
- Astrocystoma**
 Brain Neoplasms
 Urea, Methyl Nitroso-, 79-5566
 Tissue Culture
 Ultrastructural Study, 79-5566
- Ataxia Telangiectasia**
 Radiation, Ionizing
 Chromosome Aberrations, 79-5851
 Chromosomes, Review, 79-5444
- Australia Antigen**
 Hepatoma
 Liver Cirrhosis, 79-5959
- Autoimmune Diseases**
 Lymphosarcoma
 Pure Red Cell Aplasia, 79-5862
 Paraproteins
 Isolation and Characterization, Review
 79-5464
- Azathioprine**
 Lymphoma
 Case Report, 79-5863
- Bacteria**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Metabolism, Rat, 79-5532
 Cholanthrene, 3-Methyl-
 Metabolism, Rat, 79-5532
- Bacteriophages**
 Carcinogen, Chemical
 Mutation, Review, 79-5424
 Virus, SV40
 Nucleic Acid Hybridization, 79-5799
 Transformation, Genetic, 79-5799
- Barbituric Acid, 5-Ethyl-5-phenyl-**
 Aflatoxin B1
 Carcinogenic Metabolite, 79-5618
 Bacteria
 Metabolism, Rat, 79-5532
 Benzene, (Epoxyethyl)-
 Microsomes, Liver, 79-5602
 Benzo(a)pyrene
 Ames Test, 79-5609
 1,1'-Biphenyl, 2,2',5,5'-Tetrachloro-
 Proteins, Binding, 79-5616
 Cytochrome P-450
 Microsomes, Liver, 79-5638
 Drugs
 Carcinogenic Potential, Review
 79-5402
 Furan, 2-(*N*-Ethylcarbamoyloxymethyl)-
 Carcinogenic Metabolite, 79-5618
 Microsomes
 Aryl Hydrocarbon Hydroxylases
 79-5532
 NADPH Cytochrome C Reductase
 79-5532
 UDP Glucuronosyltransferase, 79-5532
 Oxidoreductases
 Liver, Rat Fetus, 79-5638
- BCC**
 Colonic Neoplasms
 Growth, 79-5843
 Hepatoma
 Virus, Avian Leukosis, 79-5704
 Lupus Erythematosus, Discoid
 Vaccine Therapy, 79-5884
 Neoplasm Transplantation
 Necrosis, Review, 79-5459
 Neoplasms, Experimental
 Immunity, Cellular, 79-5459
 Papilloma
 Nucleotides, Cyclic, 79-5632
- Benz(a)anthracene**
 Aryl Hydrocarbon Hydroxylases
 Cytochrome P-450, 79-5657
 Microsomes, 79-5657
- Benz(a)anthracene, 3,4-Dihydro-3,4-**
 dihydroxy-
 Lung Neoplasms
 Carcinogenic Metabolite, 79-5634
- Benz(a)anthracene, 3,4-Dihydroxy-1,2-oxy-**
 1,2,3,4-tetrahydro-
 Lung Neoplasms
 Carcinogenic Metabolite, 79-5634
- Benz(a)anthracene-7,12-dimethanol**
 Microsomes, Liver
 Phenol Metabolites, 79-5631
- Benz(a)anthracene, 7,12-Dimethyl-**
 Adrenal Glands
 Tissue Distribution, Rat, 79-5635
 Ames Test
 S9 Fraction, 79-5629
 Aryl Hydrocarbon Hydroxylases
 Cytochrome P-450, 79-5657
 Microsomes, 79-5657
 Cell Membrane
 Cell Transformation, Neoplastic
 79-5627
 Ultrastructural Study, Microvilli
 79-5627

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)
Endonucleases

- Cell Transformation, Neoplastic 79-5628
 - Hypothalamus
 - Tissue Distribution, Rat, 79-5635
 - Lung Neoplasms
 - Adenoma, 79-5553
 - Piperonyl Butoxide, 79-5553
 - Lymphoma
 - Piperonyl Butoxide, 79-5553
 - Virus, Murine Leukemia, 79-5728
 - Mammary Neoplasms, Experimental
 - Collagen, 79-5636
 - Propionitrile, 3-Amino-, 79-5636
 - Receptors, Hormone, 79-5637
 - Microsomes, Liver
 - Phenol Metabolites, 79-5631
 - Mouth Neoplasms
 - Carcinoma, Epidermoid, 79-5630
 - Radiation, Ionizing, 79-5685
 - Mutagenic Metabolite
 - Fetal Tissues, Mouse, Rat, 79-5629
 - Skin Neoplasms
 - Papilloma, 79-5632, 79-5633
 - Thymus Neoplasms
 - Lymphoma, 79-5728
 - Tongue Neoplasms
 - Papilloma, 79-5685
 - Virus, C-Type RNA Tumor
 - Binding, 79-5753
 - Virus, Simian Adeno 7
 - Cell Transformation, Neoplastic 79-5640
- Benz(a)anthracene-7-methanol, 12-Methyl-**
Microsomes, Liver
 - Phenol Metabolites, 79-5631
- Benz(a)anthracene-12-methanol, 7-Methyl-**
Microsomes, Liver
 - Phenol Metabolites, 79-5631
- Benzaldehyde, 4-Methyl-**
Cytochrome P-450
 - Lung, Rabbit, 79-5607
- Heme
 - Lung, Rabbit, 79-5607
- Benzene**
Chromatids
 - Lymphocytes, 79-5605
- Hodgkin's Disease
 - Occupational Hazard, 79-5932
- Leukemia, Myelocytic
 - Carcinogenic Potential, Review 79-5418
- Lymphosarcoma
 - Occupational Hazard, 79-5932
- Myelofibrosis
 - Carcinogenic Potential, Review 79-5418
- Occupational Hazard
 - Chromosome Aberrations, 79-5605
 - Epidemiology, 79-5932
- Radioisotopes
 - Chromosome Aberrations, 79-5605
- Sarcoma, Reticulum Cell
 - Occupational Hazard, 79-5932
- Benzene, 1-Chloro-2,4-dinitro-**
Breast Neoplasms
 - Hypersensitivity, Delayed, 79-5849
- Benzene, 1,2-Dichloro-4-nitro-**
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Glutathione Transferases, 79-5604
- Benzene, (Epoxyethyl)-**
Barbituric Acid, 5-Ethyl-5-phenyl-
Microsomes, Liver, 79-5602
- Cytochrome P-450
 - Metabolism, 79-5602
- Microsomes, Liver
 - Ames Test, 79-5608
- Mutation
 - Methyl-, Chloro- Derivatives, 79-5598
 - Thioguanine Resistance, 79-5598
 - Phenol, (1,1-Dimethylethyl)-4-methoxy-

Benzene, (Epoxyethyl)- (cont'd)
Epoxide Hydratases, 79-5604

- Benzene, Ethyl-**
Benzo(a)pyrene
 - Ames Test, 79-5609
- Benzenecetic Acid, α -Methyl-4-(2-methylpropyl)-**
Lupus Erythematosus, Discoid
 - Drug Therapy, 79-5884
- Benzenecarboxiperoxoic Acid, 3-Chloro-**
Aflatoxin B1
 - DNA Adducts, 79-5620
- Aflatoxin B1, 9,10-Dihydro-9-(7-guanyl)-
10-hydroxy-
DNA Adducts, 79-5620
- Aflatoxin G1
 - DNA Adducts, 79-5620
- 1,3-Benzenediamine, 4-Methoxy-**
5,6-Benzoflavone
 - Metabolism, Liver, 79-5551
- Benzidine, N-Hydroxy-N,N'-diacetyl-**
Ames Test
 - Mutagenic Metabolite, 79-5615
- RNA, Transfer
 - Binding, 79-5615
- Benzimidazole, 5,6-Dichloro-1- β -D-ribofuranosyl-**
Virus, Adeno 2
 - RNA Replication, 79-5811
- 1,2-Benzisothiazolin-3-one, 1,1-Dioxide**
Saccharomyces cerevisiae
 - Mutagenic Activity, 79-5613
- Benzo(a)pyren-1-ol**
Ames Test
 - Mutagenic Activity, 79-5649
- 7,8-Benzoflavone
 - Ames Test, 79-5649
- Uridine Diphosphate Glucuronic Acid
 - Mutagenic Metabolite, 79-5649
- Benzo(a)pyren-3-ol**
Ames Test
 - Mutagenic Activity, 79-5649
- Benzo(a)pyrene, 7,8-Dihydro-9,10-oxy-
7,8,9,10-tetrahydro-
Carcinogenic Metabolite, 79-5653
- 7,8-Benzoflavone
 - Ames Test, 79-5649
- Cholanthrene, 3-Methyl-
Microsomes, Liver, 79-5653
- Lymphocytes
 - Metabolism, 79-5660
- Uridine Diphosphate Glucuronic Acid
 - DNA, Binding, 79-5653
 - Mutagenic Metabolite, 79-5649
- Benzo(a)pyren-9-ol**
Ames Test
 - Mutagenic Activity, 79-5649
- Cholanthrene, 3-Methyl-
Microsomes, Liver, 79-5653
- Monocytes
 - Metabolism, 79-5660
- Uridine Diphosphate Glucuronic Acid
 - DNA, Binding, 79-5653
- Benzo(a)pyrene**
Ames Test
 - Mutagenic Metabolite, 79-5647
- S9 Fraction, 79-5629
- Aryl Hydrocarbon Hydroxylases
 - Cell Transformation, Neoplastic 79-5657
- DNA, Binding, 79-5648
- Ovary, Mouse, 79-5658
- Barbituric Acid, 5-Ethyl-5-phenyl-
Ames Test, 79-5609
- Benzene, Ethyl-
Ames Test, 79-5609
- 7,8-Benzoflavone
 - Ames Test, 79-5646
- Cell Division

Benzo(a)pyrene (cont'd)
Aryl Hydrocarbon Hydroxylases 79-5621

- Hepatocytes, Rat, 79-5621
- Cytochrome P-450
 - Mutagenic Metabolite, 79-5647
- Ellipticine, 9-Hydroxy-
Ames Test, 79-5646
- Environmental Hazard
 - Epidemiology, Review, 79-5433
- Glucuronidase
 - Phenol Metabolites, 79-5651
- Harman
 - Metabolism, Lung, 79-5655
- Hyperplasia
 - 2-Butanone, 79-5654
 - Croton Oil, 79-5654
 - Toluene, 79-5654
- Lymphocytes
 - Mutagenic Activity, 79-5650
- Microsomes
 - Metabolism, Fibroblasts, 79-5657
- Mutagenic Activity
 - Dose-Response Study, Review 79-5445
- Norharman
 - Metabolism, Lung, 79-5655
- Nuclear Enlargement
 - Epidermis, Mouse, 79-5654
- Styrene
 - Ames Test, 79-5609
- Virus, C-Type RNA Tumor
 - Binding, 79-5753
- Virus, Rauscher Murine Leukemia
 - Reverse Transcriptase, 79-5753
- Water Pollutants
 - Chromosome Aberrations, 79-5645
- Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy**
Carcinogenic Metabolite
 - Ovary, Mouse, 79-5658
- Glucuronidase
 - Carcinogenic Metabolite, 79-5651
- Harman
 - Metabolism, Lung, 79-5655
- Monocytes
 - Metabolism, 79-5660
- Benzo(a)pyrene, 9,10-Dihydro-9,10-dihydroxy-**
Glucuronidase
 - Carcinogenic Metabolite, 79-5651
- Benzo(a)pyrene, 7,8-Dihydro-9,10-oxy-**
7,8,9,10-tetrahydro-
Benzo(a)pyren-3-ol
 - Carcinogenic Metabolite, 79-5653
- DNA Adduct
 - Fluorescence, 79-5659
- Placenta
 - DNA Adduct, 79-5661
- Smoking
 - DNA Adduct, 79-5661
- Benzo(a)pyrene-7,8-diol-9,10-oxide**
see Benzo(a)pyrene, 7,8-Dihydro-9,10-oxy-7,8,9,10-tetrahydro-
- Benzo(a)pyrene-1,6-dione**
DNA Replication
 - Cytotoxicity, 79-5656
- Lymphocytes
 - Metabolism, 79-5660
- Oxidation-Reduction
 - Cytotoxicity, 79-5656
 - Radicals, 79-5656
- Benzo(a)pyrene-3,6-dione**
DNA Replication
 - Cytotoxicity, 79-5656
- Lymphocytes
 - Metabolism, 79-5660
- Oxidation-Reduction
 - Cytotoxicity, 79-5656
 - Radicals, 79-5656
- Benzo(a)pyrene 4,5-Oxide**
Epoxide Hydratases
 - Liver, Rat, 79-5652

- Benzo(a)pyrene 4,5-Oxide (cont'd)**
 Glutathione Transferases
 Liver, Rat, 79-5652
- 5,6-Benzoflavone**
 Acetamide, *N*-Fluoren-2-yl-
 Metabolism, Liver, 79-5551
 1,3-Benzenediamine, 4-Methoxy-
 Metabolism, Liver, 79-5551
 Fluoren-2-amine
 Metabolism, Liver, 79-5551
- 7,8-Benzoflavone**
 Aflatoxin B1
 Ames Test, 79-5646
 Benzo(a)pyren-1-ol
 Ames Test, 79-5649
 Benzo(a)pyren-3-ol
 Ames Test, 79-5649
 Benzo(a)pyrene
 Ames Test, 79-5646
 Cholanthrene, 3-Methyl-
 Ames Test, 79-5646
 Ethidium Bromide
 Ames Test, 79-5646
- Beryllium**
 Hydrolases
 Macrophages, 79-5533
- Bile Duct Neoplasms**
 Colitis
 Precancerous Conditions, 79-5912
 Liver Diseases
 Precancerous Conditions, 79-5912
- 1,1'-Biphenyl, 2,2',5,5'-Tetrachloro-**
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Proteins, Binding, 79-5616
 Microsomes, Liver
 Proteins, Binding, 79-5616
- Biphenyldiol, 4-Amino-**
 Ames Test
 Structure-Activity Relationship
 79-5617
 DNA Repair
 Mutagenic Activity, 79-5617
- Bladder Neoplasms**
 Adenoma
 Acetophenone, 2-Amino-, 79-5673
 Age Factors
 Epidemiology, France, 79-5969
 1-Butanol, 4-(Butylnitrosamino)-
 Disulfide, Bis(diethylthiocarbamoyl)-
 79-5558
 13-*cis*-Retinoic Acid, 79-5643
 Carcinoma
 Acetophenone, 2-Amino-, 79-5673
 Carcinoma In Situ
 Histopathological Study, 79-5911
 Carcinoma, Transitional Cell
 1-Butanol, 4-(Butylnitrosamino)-
 79-5643
 Genetics, 79-5910
 Occupational Hazard, 79-5910
 Smoking, 79-5910
 Environmental Hazard
 Epidemiology, France, 79-5970
 Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 Phosphine Sulfide, Tris(1-aziridinyl)-
 79-5539
 Geographic Factors
 Epidemiology, France, 79-5969
 Hyperplasia
 1-Butanol, 4-(Butylnitrosamino)-
 79-5643
 Neoplasm Seeding
 Rat, Review, 79-5486
 Neoplasms, Multiple Primary
 Smoking, 79-5970
 Phosphine Sulfide, Tris(1-aziridinyl)-
 DNA Replication, 79-5539
 Wounds and Injuries
 Cytoscopy, Review, 79-5486
- Bleomycin**
 Chromatids
 Lymphocytes, 79-5540
- Blood Circulation**
 Carcinoma
 Necrosis, 79-5994
- Bone Marrow**
 Graft vs Host Reaction
 Killer Cells, Review, 79-5460
 Histocompatibility Antigens
 Graft vs Host Reaction, Review
 79-5463
 Virus, Friend Murine Leukemia
 Cell Transformation, Neoplastic
 79-5741
- Bone Neoplasms**
 Adenocarcinoma
 Wood, 79-5971
 Carcinoma
 Osteomyelitis, 79-5887
 Radiation, Ionizing, 79-5449
 Ultrastructural Study, 79-5887
 Fibrosarcoma
 Radiation, Ionizing, 79-5449
 Giant Cell Tumors
 Ultrastructural Study, 79-5886
 Hypercalcemia
 Neoplasm Metastasis, Review, 79-5511
 Parathyroid Hormone, 79-5511
 Prostaglandins, 79-5511
 Neoplasm Metastasis
 Site Distribution, Review, 79-5479
 Osteomyelitis
 Case Report, 79-5887
 Radiation, Ionizing
 Epidemiology, Review, 79-5449
 Sarcoma
 Radiation, Ionizing, 79-5449
- Bracken Fern**
 Digestive System Neoplasms
 Diet, 79-5965
- Brain Neoplasms**
 Aluminum
 Occupational Hazard, 79-5939
 Astrocytoma
 Urea, Methyl Nitroso-, 79-5566
 Barbiturates
 Epidemiology, Children, 79-5938
 Carcinoma, Bronchogenic
 Neoplasm Metastasis, 79-5937
 Choriocarcinoma
 Neoplasm Metastasis, 79-5937
 DNA
 Cell Cycle Kinetics, 79-5995
 Flow Cytometry, 79-5995
 Ependymoma
 Virus, Polyoma, BK, 79-5791
 Epidemiology
 Kentucky, 79-5936
 Genetics
 Case Report, 79-5873
 Glioblastoma Multiforme
 Intestinal Polyps, 79-5873
 Glioma
 Urea, Methyl Nitroso-, 79-5566
 Lymphoma
 Virus, Epstein-Barr, 79-5783
 Neoplasm Metastasis
 Blacks, 79-5937
 Nerve Tissue Proteins
 Cells, Cultured, 79-5983
 Oligodendroglioma
 Urea, Methyl Nitroso-, 79-5566
 Papilloma
 Virus, Polyoma, BK, 79-5791
 Virus, Polyoma, BK
 Carcinogenic Potential, Hamster
 79-5791
- Breast Diseases**
 Adenofibroma
 Theophylline, 79-5596
 Cysts
 Theophylline, 79-5596
- Breast Diseases (cont'd)**
 Theophylline
 Nucleotides, Cyclic, 79-5596
- Breast Neoplasms**
 Adenofibroma
 Contraceptives, Oral, 79-5440
 Age Factors
 Precancerous Conditions, Review
 79-5507
 Antigens, Neoplasm
 Lymph Nodes, 79-5849
 Benzene, 1-Chloro-2,4-dinitro-
 Hypersensitivity, Delayed, 79-5849
 Carcinoma
 Immunity, Cellular, 79-5849
 Contraceptives, Oral
 Epidemiology, 79-5957
 Epidemiology, Review, 79-5441
 79-5442
 Hepatoma, 79-5440
 Diet
 Epidemiology, Japan, 79-5965
 Epidemiology
 Kentucky, 79-5936
 Estradiol
 Receptors, Hormone, 79-5637
 Estriol
 Pregnancy, 79-5508
 Genetics
 Tumor Laterality, 79-5947
 Geographic Factors
 Epidemiology, Finland, 79-5956
 Hair Dyes
 Carcinogenic Potential, 79-5950
 Hyperplasia
 Epidemiology, Review, 79-5507
 Precancerous Conditions, Review
 79-5507
 Lactation
 Epidemiology, Review, 79-5508
 Pituitary Gland
 Neoplasm Metastasis, 79-5871
 Precancerous Conditions
 Immunity, Cellular, 79-5849
 Pregnancy
 Epidemiology, Review, 79-5508
 Progesterone
 Pregnancy, 79-5508
 Reserpine
 Epidemiology, Review, 79-5435
 Socioeconomic Factors
 Epidemiology, Finland, 79-5956
 Fertility, 79-5956
 Tuberculin
 Hypersensitivity, Delayed, 79-5849
 Virus, Murine Mammary Tumor
 Nucleic Acid Hybridization, Review
 79-5458
 Virus-Like Particles, Review, 79-5508
- Bronchial Neoplasms**
 Carcinoma
 Asbestosis, 79-5975
- Brucella abortus**
 Virus, Rauscher Murine Leukemia
 Cellularity, Spleen, 79-5756
 Megakaryocytes, Plasma Cells
 79-5756
- Burkitt's Lymphoma**
 Virus, Epstein-Barr
 Antigens, Viral, 79-5781
 DNA, Viral, 79-5780, 79-5781
 79-5782
 Nucleic Acid Hybridization, 79-5782
- Bursa of Fabricius**
 Virus, Rous-Associated
 Antigens, Viral, 79-5718
- Busulfan**
 see 1,4-Butanediol, Dimethylsulfonate
- 2,3-Butanediol, 1,4-Dimercapto-**
 Radiation, Ionizing
 DNA Repair, 79-5688

1,4-Butanediol, Dimethylsulfonate
Ames Test
Microsomes, Liver, 79-5574
Chromatids
Chromosome Aberrations, 79-5573
Lymphocytes, 79-5573
Methanesulfonic Acid, Methyl Ester
Alkaline Elution Assay, 79-5577

1-Butanol, 4-(Butylnitrosamino)-
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-5643
Disulfide, Bis(diethylthiocarbamoyl)-
79-5558
Hyperplasia, 79-5643
13-*cis*-Retinoic Acid, 79-5643

2-Butanone
Hyperplasia
Benzo(a)pyrene, 79-5654

1-Butanone, 4-(Methylnitrosamino)-1-(3-pyridyl)-
Ames Test
Hydroxy Derivatives, Review, 79-5414
Respiratory Tract Neoplasms
Tobacco Alkaloids, Review, 79-5414

tert-Butyl-4-hydroxyanisole
see Phenol, (1,1-Dimethylethyl)-4-methoxy-

Butyric Acid, 4-Amino-
Glioma
Peptide Synthesis, 79-5980

Butyric Acid, α -Aminoiso-
see Alanine, 2-Methyl-

Butyric Acid, 4-(p-Bis(2-chloroethyl)aminophenyl)-
Chromatids
Cell Cycle Kinetics, 79-5540
Lymphocytes, 79-5540

Cadmium
Occupational Hazard
Toxicity, 79-5935

Caffeine
Radiation, Ionizing
DNA Photolyase, 79-5688
Escherichia coli, 79-5688
Ultraviolet Rays
DNA Photolyase, 79-5688

Calcium Oxide
Mouth Neoplasms
Retinol Palmitate, 79-5535

Camptothecin
Virus, Rous Sarcoma
Cytochrome Oxidase, 79-5714

Carbamic Acid, Diethyldithio-
Pyrrolidine, 1-Nitroso-
Metabolism, 79-5578

Carbamic Acid, Ethyl Ester
Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor
79-5734

Carbohydrates
Teratoid Tumor
Cell Adhesion, 79-5989
Cell Membrane, 79-5989

Carbon Tetrachloride
Environmental Hazard
Epidemiology, Review, 79-5433

Carcinogen, Chemical
Air Pollution
Risk Evaluation, Review, 79-5510
Ames Test
Mutation, Review, 79-5424
Review, 79-5423
Bacteriophages
Mutation, Review, 79-5424
Drugs
Animal Feed, Review, 79-5427

Carcinogen, Chemical (cont'd)
Electrophilic Metabolites
Screening Tests, Review, 79-5422
Environmental Hazard
Risk Evaluation, Review, 79-5429
Escherichia coli
Mutation, Review, 79-5424
Genetics
Risk Factors, Review, 79-5474
Hepatitis
Diagnosis, Review, 79-5426
Hepatoma
Alpha Fetoproteins, 79-5467
Antigenic Determinants, Review
79-5467
Enzymatic Activity, 79-5703
Liver Neoplasms
Occupational Hazard, Review, 79-5426
Mathematical Model
Dose-Response Study, Review
79-5419
Mutation
Threshold Limit Values, Review
79-5445
Neoplasms, Experimental
Dose-Response Study, Review
79-5419
Human Risk Factors, Review, 79-5425
Mouse, Nude, Review, 79-5471
Nucleic Acids
Mutagenic Activity, Review, 79-5422
Occupational Hazard
Risk Evaluation, Review, 79-5510
Teratogenic Effect, Review, 79-5437
Saccharomyces cerevisiae
Cytochromes, 79-5514
Mitochondria, 79-5514
Mutagenic Activity, 79-5514
Selenium
Metabolism, Review, 79-5405
Spermatozoa
Morphology, Review, 79-5421
Urogenital Neoplasms
DNA Repair, Review, 79-5420

Carcinogen, Environmental
Bioassays
Risk Evaluation, Review, 79-5431
Hereditary Diseases
Risk Factors, Review, 79-5474
Liver Neoplasms
Kupffer Cells, Review, 79-5482
Phagocytosis
Kupffer Cells, Review, 79-5482
Structure-Activity Relationship
Risk Evaluation, Review, 79-5431

Carcinoid Tumor
Intestinal Neoplasms
Case Report, 79-5903, 79-5905

Carcinoma
Bladder Neoplasms
Acetophenone, 2-Amino-, 79-5673
Blood Circulation
Necrosis, 79-5994
Bone Neoplasms
Osteomyelitis, 79-5887
Radiation, Ionizing, 79-5449
Ultrastructural Study, 79-5887
Breast Neoplasms
Immunity, Cellular, 79-5849
Bronchial Neoplasms
Asbestosis, 79-5975
Cervix Neoplasms
Immunity, Cellular, 79-5850
Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -
Isomer
Carcinogenic Potential, Rat, 79-5417
Intestinal Neoplasms
Polyps, 79-5906
Liver Neoplasms
Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -
Isomer, 79-5417
Lung Neoplasms
Immunity, Cellular, 79-5845
Smoking, 79-5963
Meningeal Neoplasms

Carcinoma (cont'd)
Case Report, 79-5874
Neoplasm Transplantation
Growth, 79-5994
Necrosis, 79-5994
Ovarian Neoplasms
Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -
Isomer, 79-5417
Parotid Neoplasms
Neoplasms, Multiple Primary, 79-5872
Pituitary Neoplasms
Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -
Isomer, 79-5417
Rectal Neoplasms
Epidemiology, 79-5958
Polyps, 79-5909
Stomach Neoplasms
Precancerous Conditions, 79-5504
Thyroid Neoplasms
Neoplastic Endocrine-Like Syndromes
79-5868

Carcinoma, Basal Cell
Nevus, Pigmented
Precancerous Conditions, Review
79-5480
Skin Neoplasms
Arsenic, 79-5534
Ultraviolet Rays
Age Factors, Review, 79-5446

Carcinoma, Bronchiolar
Lung Neoplasms
Smoking, 79-5963

Carcinoma, Bronchogenic
Brain Neoplasms
Neoplasm Metastasis, 79-5937

Carcinoma, Ductal
Liver Neoplasms
Precancerous Conditions, Review
79-5491
Pancreatic Neoplasms
Epidemiology, Review, 79-5501

Carcinoma, Ehrlich Tumor
Graft Survival
Kidney, Hypertrophic, 79-5915
Quinoline, 4-Nitro-, 1-Oxide
Sulphydryl Compounds, 79-5592

Carcinoma, Epidermoid
Cervix Neoplasms
Case Report, 79-5923
Cholanthrene, 3-Methyl-
Neoplasm Transplantation, 79-5641
Esophageal Neoplasms
Diverticulosis, 79-5895
Epidemiology, France, 79-5967
Epidemiology, Nigeria, 79-5961
Esophagitis, Peptic, 79-5897
Scleroderma, Systemic, 79-5894
Eye Neoplasms
Case Report, 79-5876
Classification, Review, 79-5477
Gynecologic Neoplasms
Epidemiology, 79-5953
Laryngeal Neoplasms
Epidemiology, 79-5888
Genetics, 79-5888
Lung Neoplasms
Acetophenone, 2-Amino-, 79-5673
Immunity, Cellular, 79-5845
Smoking, 79-5963
Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
1-nitroso-, 79-5571
Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-
nitroso-, 79-5571
Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-5630
Nose Neoplasms
Cesium Radioisotopes, 79-5684
Strontium, 79-5684
Yttrium Radioisotopes, 79-5684
Pharyngeal Neoplasms
Diverticulosis, 79-5895
Surface Properties

- Carcinoma, Epidermoid (cont'd)**
 Ascitic Tumor, 79-5641
 Tracheal Neoplasms
 Arsenic, 79-5534
 Ultraviolet Rays
 Age Factors, Review, 79-5446
 Urogenital Neoplasms
 Dipropylamine, 2,2'-Dioxo-*N*-nitroso-
 79-5564
 Yttrium Radioisotopes
 Inhalation Study, Dog, 79-5684
- Carcinoma In Situ**
 Bladder Neoplasms
 Histopathological Study, 79-5911
 Cervix Neoplasms
 Condylomata Acuminata, 79-5921
 Contraceptives, Oral, 79-5440
 Esophageal Neoplasms
 Esophagitis, Peptic, 79-5897
 Rectal Neoplasms
 Polyps, 79-5909
- Carcinoma, Papillary**
 Mammary Neoplasms, Experimental
 Estrone, 79-5997
 Progesterone, 79-5997
- Carcinoma, Transitional Cell**
 Bladder Neoplasms
 1-Butanol, 4-(Butylnitrosamino)-
 79-5643
 Genetics, 79-5910
 Occupational Hazard, 79-5910
 Smoking, 79-5910
 Genetics
 Case Report, 79-5910
 Kidney Neoplasms
p-Acetophenetide, 79-5612
- Carcinoma 256, Walker**
 Intestines, Small
 Growth, 79-5691
 Neoplasm Transplantation, 79-5691
 Lymph Nodes
 Lymphatic Metastasis, 79-5865
- Carrier Proteins**
 Virus, Adeno 2
 DNA, Viral, 79-5809
 Virus, Adeno 5
 DNA, Viral, 79-5809
- Catecholamines**
 12-*O*-Tetradecanoylphorbol-13-acetate
 Adenosine Cyclic 3',5' Monophos-
 phate, 79-5625
- Cell Adhesion**
 Teratoid Tumor
 Carbohydrates, 79-5989
- Cell Differentiation**
 Cell Transformation, Neoplastic
 Gene Regulation, Review, 79-5473
 Colonic Neoplasms
 Formamide, *N,N*-Dimethyl-, 79-5999
 Leukemia, Myeloblastic
 Hematopoietic Stem Cells, 79-5859
 Leukemia, Myelocytic
 Antigens, Neoplasm, 79-5824
 Mammary Neoplasms, Experimental
 Formamide, *N,N*-Dimethyl-, 79-5999
 Metaplasia
 Gene Regulation, Review, 79-5473
 Neuroblastoma
 Glycoproteins, 79-5984
 Rhabdomyosarcoma
 Formamide, *N,N*-Dimethyl-, 79-5999
 Teratoid Tumor
 Collagen, 79-5990
 Virus, Friend Murine Leukemia
 Hematopoietic Stem Cells, 79-5741
 Virus, Friend Spleen Focus-Forming
 Hematopoietic Stem Cells, 79-5741
 Virus, Kirsten Murine Sarcoma
 Hematopoietic Stem Cells, 79-5741
- Cell Division**
 Aflatoxin B1
- Cell Division (cont'd)**
 Aryl Hydrocarbon Hydroxylases
 79-5621
 Hepatocytes, Rat, 79-5621
 Benzo(a)pyrene
 Aryl Hydrocarbon Hydroxylases
 79-5621
 Hepatocytes, Rat, 79-5621
 Melanocytes
 Aging, 79-5992
 Choroid, Monkey, 79-5992
- Cell Membrane**
 Benz(a)anthracene, 7,12-Dimethyl-
 Cell Transformation, Neoplastic
 79-5627
 Ultrastructural Study, Microvilli
 79-5627
 Teratoid Tumor
 Carbohydrates, 79-5989
 Virus, Friend Murine Leukemia
 Antigens, 79-5743
 Virus, Murine Mammary Tumor
 Antigens, Viral, 79-5735
- Cell Survival**
 Ultraviolet Rays
 Chromosome Aberrations, 79-5680
- Cell Transformation, Neoplastic**
 Actin
 Mouse, Nude, Review, 79-5469
 Adenoma
 Intestinal Polyps, 79-5902
 Benz(a)anthracene, 7,12-Dimethyl-
 Cell Membrane, 79-5627
 Endonucleases, 79-5628
 Benzo(a)pyrene
 Aryl Hydrocarbon Hydroxylases
 79-5657
 Cell Differentiation
 Gene Regulation, Review, 79-5473
 Cycloheximide
 Phenotype, 79-5746
 Ethacryl
 Connective Tissue, 79-5677
 Intestinal Neoplasms
 Adenoma, 79-5902
 Leukocytes
 Transplantation, Heterologous
 79-5826
 Melanoma
 Nevus, Pigmented, 79-5878
 Neuroglia
 Cells, Cultured, 79-5983
 Nerve Tissue Proteins, 79-5983
 Oncogenic Viruses
 Mouse, Nude, Review, 79-5470
 Plasminogen Activators
 Mouse, Nude, Review, 79-5469
 Transplantation, Heterologous
 Mouse, Nude, Review, 79-5470
 Urea, Ethyl Nitroso-
 Brain, Fetal Rat, 79-5569
 Ultrastructural Study, 79-5569
 Virus, Abelson Murine Leukemia
 Antigenic Determinants, 79-5760
 Virus, Helper, 79-5737
 Virus, Adeno 5
 Temperature Sensitive Mutants
 79-5815
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-5815
 Virus Replication, 79-5772
 Virus, Avian Reticuloendotheliosis
 B-Lymphocytes, 79-5719
 Virus, Avian Sarcoma
 Phosphoproteins, 79-5707
 Virus, Bovine Papilloma
 Cells, Cultured, 79-5762
 Virus, Feline Sarcoma
 Antigenic Determinants, 79-5760
 Virus, Friend Murine Leukemia
 Bone Marrow, 79-5741
 Virus, Harvey Murine Sarcoma
 Fibroblasts, 79-5749
 Virus, Herpes Simplex 2
 DNA, Viral, 79-5773
- Cell Transformation, Neoplastic (cont'd)**
 Ultraviolet Rays, 79-5773, 79-5775
 Virus, Kirsten Murine Sarcoma
 DNA, Viral, 79-5745
 Fibroblasts, 79-5749
 Peptides, 79-5748
 Virus, Mink Cell Focus-Inducing
 Antigenic Determinants, 79-5760
 Virus, Polyoma, BK
 Karyotyping, 79-5790
 RNA, Messenger, 79-5789
 Virus, Rat Sarcoma
 Fibroblasts, 79-5749
 Virus, Rous Sarcoma
 DNA, Viral, 79-5709
 Genes, Viral, 79-5713
 Procollagen, 79-5716
 Virus, Simian Adeno 7
 Benz(a)anthracene, 7,12-Dimethyl-
 79-5640
 Cholanthrene, 3-Methyl-, 79-5640
 Virus, SV40
 DNA, Single Stranded, 79-5798
 Xanthine Oxidase
 Enzymatic Activity, 79-5978
- Cells, Cultured**
 Brain Neoplasms
 Nerve Tissue Proteins, 79-5983
 Chromosome Aberrations
 Chromium Trioxide, 79-5536
 Micronucleus Test, 79-5851
 Neuroblastoma
 Acetylcholinesterase, 79-5984
 Choline Acetyltransferase, 79-5984
 Neuroglia
 Cell Transformation, Neoplastic
 79-5983
 Virus, Avian Reticuloendotheliosis
 Tumorigenicity, 79-5719
 Virus, Bovine Papilloma
 Cell Transformation, Neoplastic
 79-5762
 Virus, Polyoma, BK
 Tumorigenicity, 79-5790
- Cellular Inclusions**
 Virus, Herpes Simplex 2
 Ultraviolet Rays, 79-5774
- Ceruloplasmin**
 Liver Neoplasms
 Growth, 79-5998
 Oxidoreductases, 79-5998
 Mammary Neoplasms, Experimental
 Growth, 79-5998
 Oxidoreductases, 79-5998
- Cervix Neoplasms**
 Antigenic Determinants
 Isolation and Characterization
 79-5776
 Carcinoma
 Immunity, Cellular, 79-5850
 Carcinoma, Epidermoid
 Case Report, 79-5923
 Carcinoma In Situ
 Condylomata Acuminata, 79-5921
 Contraceptives, Oral, 79-5440
 Condylomata Acuminata
 Precancerous Conditions, 79-5921
 Contraceptives, Oral
 Epidemiology, Review, 79-5509
 Hepatoma, 79-5440
 Diet
 Epidemiology, Japan, 79-5965
 Retinol, 79-5965
 Digestive System Neoplasms
 Epidemiology, Japan, 79-5965
 Irrigation
 Epidemiology, 79-5952
 Papilloma
 Case Report, 79-5923
 Polyps
 Precancerous Conditions, 79-5922
 Precancerous Conditions
 Epidemiology, 79-5922
 Immunity, Cellular, 79-5850

Cervix Neoplasms (cont'd)
Sex Behavior, Review, 79-5509

Vasectomy
Epidemiology, 79-5951

Virus, Herpes Simplex 2
Antigenic Determinants, 79-5776
Sex Behavior, Review, 79-5509

Cesium Radioisotopes
Nose Neoplasms
Carcinoma, Epidermoid, 79-5684
Radioactive Fallout
Greenland, 79-5927

Chloramphenicol
Guanidine, 1-Methyl-3-nitro-1-nitroso-DNA Repair, 79-5589
Virus, Rous Sarcoma
Cytochrome Oxidase, 79-5714

Chloroma
see Leukemia, Myelocytic

Cholanthren-2-ol, 3-Methyl-Lactation
Carcinogenic Metabolite, 79-5642

Cholanthrene, 1,2-Dihydroxy-3-methyl-Lactation
Carcinogenic Metabolite, 79-5642

Cholanthrene, 3-Methyl-
Alpha Fetoproteins
Hepatotoxicity, 79-5552
Aryl Hydrocarbon Hydroxylases
Hepatocytes, Rat, 79-5621
Microsomes, Liver, 79-5609

Bacteria
Metabolism, Rat, 79-5532

Benzo(a)pyren-3-ol
Microsomes, Liver, 79-5653

Benzo(a)pyren-9-ol
Microsomes, Liver, 79-5653

7,8-Benzoflavone
Ames Test, 79-5646

Carcinoma, Epidermoid
Neoplasm Transplantation, 79-5641

Cytochrome P-450
Microsomes, Liver, 79-5638

Ellipticine, 9-Hydroxy-
Ames Test, 79-5646

Epoxide Hydratases
Microsomes, Liver, 79-5609

Fibrosarcoma
Immune Response, Rat, 79-5639
Immunity, Cellular, 79-5834

Lung Neoplasms
Adenocarcinoma, 79-5642
Adenoma, 79-5642
Horizontal Transmission, Milk
79-5642

Lymphoma
Antigen-Antibody Reactions, 79-5835

Microsomes
Aryl Hydrocarbon Hydroxylases
79-5532
NADPH Cytochrome C Reductase
79-5532
UDP Glucuronosyltransferase, 79-5532

Oxidoreductases
Liver, Rat Fetus, 79-5638

Prostate
Metaplasia, 79-5644

Prostatic Hypertrophy
Retinoic Acid, 79-5644

Sarcoma
Antibody Specificity, 79-5835
Neoplasm Transplantation, 79-5641

Sarcoma, Jensen
Immune Response, Rat, 79-5639

Virus, C-Type RNA Tumor
Binding, 79-5753

Virus, Simian Adeno 7
Cell Transformation, Neoplastic
79-5640

Cholesterol
Colonic Neoplasms
Metabolism, Review, 79-5505

Cholesterol (cont'd)
Teratoid Tumor
Metabolism, 79-5988

Choline Acetyltransferase
Neuroblastoma
Cells, Cultured, 79-5984

Cholinesterases
Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
Plasma Enzymes, 79-5529

Chondrosarcoma
Radiation, Ionizing
Epidemiology, Review, 79-5449

Choriocarcinoma
Brain Neoplasms
Neoplasm Metastasis, 79-5937
Eye Neoplasms
Neoplasm Metastasis, 79-5920
Neoplasm Metastasis
Case Report, 79-5920
Ovarian Neoplasms
Neoplasm Metastasis, 79-5920

Chromatids
Adriamycin
Chromosome Aberrations, 79-5573
Lymphocytes, 79-5573

Benzene
Lymphocytes, 79-5605

Bleomycin
Lymphocytes, 79-5540

1,4-Butanediol, Dimethylsulfonate
Chromosome Aberrations, 79-5573
Lymphocytes, 79-5573

Butyric Acid, 4-(*p*-Bis(2-chloroethyl)aminophenyl)-
Cell Cycle Kinetics, 79-5540
Lymphocytes, 79-5540

Cyclophosphamide
Chromosome Aberrations, 79-5573
79-5575
Lymphocytes, 79-5573

Cytosine, 1- β -D-Arabinofuranosyl-
Lymphocytes, 79-5540

Dichromic Acid, Dipotassium Salt
Chromosome Aberrations, 79-5537

Dichromic Acid, Disodium Salt
Chromosome Aberrations, 79-5537

Methotrexate
Lymphocytes, 79-5540

Mitomycin C
Cell Cycle Kinetics, 79-5540
Lymphocytes, 79-5540, 79-5675

Phosphine Sulfide, Tris(1-aziridinyl)-
Chromosome Aberrations, 79-5575
Lymphocytes, 79-5540

Radiation, Ionizing
Lymphocytes, 79-5675

Toluene
Lymphocytes, 79-5605

Ultraviolet Rays
Psoralen, 4,5',8-Trimethyl-, 79-5692
Xeroderma Pigmentosum, 79-5680

Chromatin
Ethane, 1,2-Dibromo-Spermatzoa, 79-5521

Hepatoma
Virus, Avian Leukosis, 79-5700

Virus, SV40
DNA, Viral, 79-5794
Histones, 79-5802
Viral Proteins, 79-5802

Chromium Trioxide
Cells, Cultured
Chromosome Aberrations, 79-5536

Dichromic Acid, Dipotassium Salt
Chromosome Aberrations, 79-5536

Nickel Sulfide
Chromosome Aberrations, 79-5536

Chromosome Aberrations
Adelphane
Antihypertensive Agents, 79-5611

Chromosome Aberrations (cont'd)
Mitosis, 79-5611

Adriamycin
Chromatids, 79-5573

Anemia, Aplastic
Radiation, Ionizing, 79-5851

Ataxia Telangiectasia
Radiation, Ionizing, 79-5851

Benzene
Occupational Hazard, 79-5605

Benzo(a)pyrene
Water Pollutants, 79-5645

1,4-Butanediol, Dimethylsulfonate
Chromatids, 79-5573

Cells, Cultured
Chromium Trioxide, 79-5536
Micronucleus Test, 79-5851

Cyclophosphamide
Chromatids, 79-5573, 79-5575

Dichromic Acid, Dipotassium Salt
Chromatids, 79-5537
Chromium Trioxide, 79-5536

Dichromic Acid, Disodium Salt
Chromatids, 79-5537

Dimethylamine, *N*-Nitroso-
Lymphocytes, 79-5575

Down's Syndrome
Radiation, Ionizing, 79-5851

Dwarfism
Radiation, Ionizing, 79-5851

Ethylene, Chloro-
Lymphocytes, 79-5575

Ethyleneimine
Lymphocytes, 79-5530

Fotrin
Lymphocytes, 79-5530

Gallic Acid, Propyl Ester
Plants, 79-5603
Radiation, Ionizing, 79-5603

Hereditary Diseases
Radiation Tolerance, Review, 79-5444

Imidazole-1-ethanol, 2-Methyl-5-nitro-
Lymphocytes, 79-5586, 79-5587
Urinary Metabolite, 79-5586

Leukemia, Lymphoblastic
Drug Therapy, 79-5513
Radiation, Ionizing, 79-5513

Leukemia, Myeloblastic
Drug Therapy, 79-5513

Leukemia, Myelocytic
Drug Therapy, 79-5513

Lymphocytes
Cell Cycle Kinetics, 79-5530

Meningioma
Chromosomes, Human, 21-22, 79-5806

Methotrexate
Radiotherapy, 79-5512

Mitomycin C
Down's Syndrome, 79-5675
Lymphocytes, 79-5675

Nickel Sulfide
Chromium Trioxide, 79-5536

Phenol, (1,1-Dimethylethyl)-4-methoxy-
Radiation, Ionizing, 79-5603

Phenol, 4-Methoxy-
Radiation, Ionizing, 79-5603

Phosphamide
Lymphocytes, 79-5530

Phosphine Oxide, 1,4-
Piperazinediylbis(bis(1-aziridinyl))-
Lymphocytes, 79-5530

Phosphine Sulfide, Tris(1-aziridinyl)-
Chromatids, 79-5575
Lymphocytes, 79-5530

3,6-Pyridazinedione, 1,2-Dihydro-
Hamster V79 Cells, 79-5610

Potassium, Diethanolamine Salts
79-5610

Radiation, Ionizing
Down's Syndrome, 79-5675
Lymphocytes, 79-5675

Radioactive Fallout
G-Banding, 79-5681

Radioisotopes
Benzene, 79-5605
Occupational Hazard, 79-5605

Radon

- Chromosome Aberrations (cont'd)**
 Lymphocytes, 79-5679
 Water Supply, 79-5679
Toluene
 Occupational Hazard, 79-5605
Trophoblastic Tumor
 Drug Therapy, 79-5512
 Radiotherapy, 79-5512
Ultraviolet Rays
 Cell Survival, 79-5680
 Mitosis, 79-5680
 Urea, Methyl Nitroso-
 Lymphocytes, 79-5575
 Water Pollutants
 Lymphocyte Culture Technique
 79-5645
- Chromosome Abnormalities**
 Melanoma
 Transplantation, Heterologous
 79-5991
- Chromosomes**
Hepatoma
 Morris Tumor, Review, 79-5407
Melanoma
 Hybrid Cells, 79-5839
 Virus, Epstein-Barr
 Virus Activation, 79-5781
- Chromosomes, Human**
 Hybrid Cells
 Tumorigenicity, 79-5852
- Chromosomes, Human, 13-15**
 Retinoblastoma
 Chromosomes, Human, 21-22, 79-5476
 Genetics, Review, 79-5476
- Chromosomes, Human, 21-22**
 Leukemia, Myelocytic
 Blast Crisis, 79-5827
 Meningioma
 Chromosome Aberrations, 79-5806
 Retinoblastoma
 Chromosomes, Human, 13-15, 79-5476
- 6-Chrysenamine**
 Alpha Fetoproteins
 Hepatotoxicity, 79-5552
- Cicatrix**
 Lung Neoplasms
 Rib Fracture, 79-5695
- Cimetidine**
 Stomach Neoplasms
 Glycoproteins, 79-5416
 Nitroso Derivative, Review, 79-5415
 79-5416
- Clomid**
see Triethylamine, 2-(p-(2-Chloro-1,2-diphenylvinyl)phenoxy)-, C
- Collitis**
 Bile Duct Neoplasms
 Precancerous Conditions, 79-5912
- Colitis, Ulcerative**
 Colonic Neoplasms
 Case Report, 79-5907
- Collagen**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-
 79-5636
 Teratoid Tumor
 Basement Membrane, 79-5990
 Cell Differentiation, 79-5990
 Peptides, 79-5990
- Colonic Neoplasms**
 Adenocarcinoma
 Glycoproteins, 79-6000
 Antineoplastic Agents
 Clone Cells, 79-5999
BCG
 Growth, 79-5843
 Cholesterol
 Metabolism, Review, 79-5505
- Colonic Neoplasms (cont'd)**
 Colitis, Ulcerative
 Case Report, 79-5907
 Diet
 Epidemiology, Netherlands, 79-5506
 Dietary Fiber
 Epidemiology, Review, 79-5505
 Formamide, N,N-Dimethyl-
 Cell Differentiation, 79-5999
 Glucosamine
 Membrane Proteins, 79-6000
 Glycoproteins
 Concanavalin A, 79-6000
 Oligosaccharides, 79-6000
 Hydrazine, 1,2-Dimethyl-
 Neoplasm Transplantation, 79-5843
 T-Lymphocytes
 Antilymphocyte Serum, 79-5547
 Neoplasms, Multiple Primary
 Hydrazine, 1,2-Dimethyl-, 79-5547
 Sarcoma, Reticulum Cell
 Case Report, 79-5907
 Surgery, Operative
 Immunity, Cellular, 79-5547
- Complement**
 Macrophages
 Antitumor Activity, Review, 79-5461
 Virus, Herpes Simplex
 Genetics, 79-5769
- Concanavalin A**
 Colonic Neoplasms
 Glycoproteins, 79-6000
 Corticosterone
 Lymphocytes, 79-5670
 Estradiol
 Lymphocytes, 79-5670
 4,4'-Stilbenediol, α,α' -Diethyl-
 Lymphocytes, 79-5670
 Virus, SV40
 Antigens, Neoplasm, 79-5804
 Immunization, 79-5804
 T-Lymphocytes, 79-5804
- Condylomata Acuminata**
 Cervix Neoplasms
 Carcinoma In Situ, 79-5921
 Precancerous Conditions, 79-5921
 Virus, Papilloma
 Precancerous Conditions, 79-5921
- Connective Tissue**
 Ethacryl
 Cell Transformation, Neoplastic
 79-5677
- Contact Inhibition**
 Xanthine Oxidase
 Enzymatic Activity, 79-5978
- Contraceptives, Oral**
 Breast Neoplasms
 Adenofibroma, 79-5440
 Epidemiology, 79-5957
 Epidemiology, Review, 79-5441
 79-5442
 Hepatoma, 79-5440
 Cervix Neoplasms
 Carcinoma In Situ, 79-5440
 Epidemiology, Review, 79-5509
 Hepatoma, 79-5440
 Gynecologic Neoplasms
 Epidemiology, Review, 79-5442
 Hepatoma
 Carcinogenic Potential, 79-5490
 Epidemiology, 79-5941, 79-5942
 Epidemiology, Review, 79-5436
 79-5440, 79-5441, 79-5443
 Estradiol, 17-Ethynyl-, 79-5941
 Mestranol, 79-5941
 Precancerous Conditions, 79-5942
 Liver Neoplasms
 Adenoma, 79-5441, 79-5443
 Epidemiology, Review, 79-5442
 79-5443, 79-5503
 Hyperplasia, 79-5443
 Precancerous Conditions, 79-5941
 Precancerous Conditions, Review
- Contraceptives, Oral (cont'd)**
 Precancerous Conditions, Review
 79-5440
 Melanoma
 Neoplasm Metastasis, 79-5672
 Pituitary Neoplasms
 Amenorrhea, Review, 79-5494
- Corticosterone**
 Lymphocytes
 Concanavalin A, 79-5670
 Lipopolysaccharides, 79-5670
- Cortisone**
 T-Lymphocytes
 Immune Response, Review, 79-5462
- Cortisone Acetate**
 T-Lymphocytes
 Immunity, Passive, 79-5833
- p-Cresol, 2,6-Di-tert-butyl-**
 Cytochrome P-450
 Metabolism, Liver, 79-5600
 Microsomes, Liver
 Aryl Hydrocarbon Hydroxylases
 79-5600
 Cytochrome Reductases, 79-5600
 Oxidoreductases, 79-5600
- Mutagens**
 Ames Test, 79-5599
 Enzyme Activation, 79-5599
- Croton Oil**
 Hyperplasia
 Benzo(a)pyrene, 79-5654
- Cryptorchism**
 4,4'-Stilbenediol, α,α' -Diethyl-
 Testicular Hypoplasia, 79-5671
- Cushing's Syndrome**
 Adrenal Gland Neoplasms
 Adenoma, 79-5666
- Cycasin**
 Hepatoma
 Epidemiology, Review, 79-5490
- Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -Isomer**
 Carcinoma
 Carcinogenic Potential, Rat, 79-5417
 Liver Neoplasms
 Carcinoma, 79-5417
 Ovarian Neoplasms
 Carcinoma, 79-5417
 Pituitary Neoplasms
 Carcinoma, 79-5417
- Cycloheximide**
 Alpha Globulins
 Liver, Rat, 79-5544
 RNA, Messenger, 79-5544
 Cell Transformation, Neoplastic
 Phenotype, 79-5746
 Sarcoma, Osteogenic
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-5746
 Virus, Kirsten Murine Sarcoma
 79-5746
 Virus, Herpes Simplex 1
 RNA, Messenger, 79-5770
 Virus, Herpes Simplex 2
 Virus Replication, 79-5774
 Virus, Kirsten Murine Sarcoma
 Virus Activation, 79-5747
- Cyclopenta(a)phenanthren-17-one, 15,16-Dihydro-11-methyl-**
 Carcinogenic Metabolite
 X-Ray Diffraction, 79-5597
- Cyclopenta(cd)pyrene**
 Lymphocytes
 Mutagenic Activity, 79-5650
- Cyclophosphamide**
 Ames Test
 Urinary Metabolite, 79-5574
 Chromatids

Cyclophosphamide (cont'd)
 Chromosome Aberrations, 79-5573
 79-5575
 Lymphocytes, 79-5573
Granuloma
 DNA, 79-5577
 Leukemia, Lymphocytic
 Lymphosarcoma, 79-5930

Cystadenocarcinoma
 Gynecologic Neoplasms
 DNA, 79-5996

Cystadenoma
 Ovarian Neoplasms
 Ploidies, 79-5918
 Ultrastructural Study, 79-5918

Cysteine, N-Acetyl-
 Smoking
 Thioethers, 79-5580

Cysts
 Breast Diseases
 Theophylline, 79-5596

Cytidine
 Acetamide, N-(Acetyloxy)-N-(4-(2-phenylethenyl)phenyl)-
 Adenosine, 79-5554
 Nucleoside Adducts, 79-5554

Cytidine Triphosphate
 Hepatoma
 Metabolism, Review, 79-5466

Cytochrome Oxidase
 Virus, Rous Sarcoma
 Camptothecin, 79-5714
 Chloramphenicol, 79-5714
 Ethidium Bromide, 79-5714

Cytochrome P-450
 2-Anthracenamide
 Mutagenic Metabolite, 79-5647
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Microsomes, Liver, 79-5638
 Benz(a)anthracene
 Aryl Hydrocarbon Hydroxylases
 79-5657
 Benz(a)anthracene, 7,12-Dimethyl-
 Aryl Hydrocarbon Hydroxylases
 79-5657
 Benzaldehyde, 4-Methyl-
 Lung, Rabbit, 79-5607
 Benzene, (Epoxyethyl)-
 Metabolism, 79-5602
 Benzo(a)pyrene
 Mutagenic Metabolite, 79-5647
 Cholanthrene, 3-Methyl-
 Microsomes, Liver, 79-5638
 p-Cresol, 2,6-Di-tert-butyl-
 Metabolism, Liver, 79-5600
 Ethyl Alcohol
 Microsomes, Liver, 79-5518
 Oxidoreductases
 Liver, Rat Fetus, 79-5638

Cytochrome Reductases
 p-Cresol, 2,6-Di-tert-butyl-
 Microsomes, Liver, 79-5600

Cytochromes
 Carcinogen, Chemical
Saccharomyces cerevisiae, 79-5514

Cytosine, 1-β-D-Arabinofuranosyl-
 Chromatids
 Lymphocytes, 79-5540
 Virus, Herpes Simplex 2
 Virus Replication, 79-5774

Daunomycin
 Ames Test
 Urinary Metabolite, 79-5574

Dexamethasone
 Adrenal Gland Neoplasms
 Hyperaldosteronism, 79-5662
 Hepatoma
 Binding Sites, 79-5700

Dexamethasone (cont'd)
 Thymidine Kinase, 79-5704
 Tyrosine Aminotransferase, 79-5704

Diabetes Mellitus
 Ovarian Neoplasms
 Epidemiology, 79-5955
 Uterine Neoplasms
 Pituitary Hormones, Review, 79-5485

2,4-Diaminoanisole
 see 1,3-Benzenediamine, 4-Methoxy-

Dibenz(a,h)anthracene
 Environmental Hazard
 Epidemiology, Review, 79-5433

Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-
 Aryl Hydrocarbon Hydroxylases
 Microsomes, Liver, 79-5519
 Environmental Hazard
 Epidemiology, Review, 79-5433
 Hepatoma
 Dose-Response Study, Mouse, 79-5520
 Liver Neoplasms
 Dose-Response Study, Mouse, 79-5519

Dibutyl Cyclic AMP
 Papilloma
 Nucleotides, Cyclic, 79-5632

Dichromic Acid, Dipotassium Salt
 Chromatids
 Chromosome Aberrations, 79-5537
 Chromosome Aberrations
 Chromium Trioxide, 79-5536

Dichromic Acid, Disodium Salt
 Chromatids
 Chromosome Aberrations, 79-5537

Diet
 Breast Neoplasms
 Epidemiology, Japan, 79-5965
 Cervix Neoplasms
 Epidemiology, Japan, 79-5965
 Retinol, 79-5965
 Colonic Neoplasms
 Epidemiology, Netherlands, 79-5506
 Digestive System Neoplasms
 Bracken Fern, 79-5965
 Lung Neoplasms
 Epidemiology, Japan, 79-5965
 Neoplasms
 Epidemiology, Review, 79-5496
 Pancreatitis
 Epidemiology, 79-5972

Dietary Fiber
 Colonic Neoplasms
 Epidemiology, Review, 79-5505

Diethylamine, 2,2'-Dichloro-N-methyl-
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 DNA Repair, 79-5586

Diethylamine, 2,2'-Dichloro-N-methyl-, N-Oxide
 Ames Test
 Urinary Metabolite, 79-5574

Diethylamine, N-Nitroso-
 Adenosine Cyclic 3',5' Monophosphate
 Protein Kinase, 79-5563
 Food Contamination
 Carcinogenic Potential, Review
 79-5412
 Hepatoma
 DNA Replication, 79-5561
 Precancerous Conditions, 79-5489
 Liver Neoplasms
 Animal Model, Fish, 79-5560
 Histological Study, 79-5560
 Ornithine Decarboxylase
 Liver, Rat, 79-5563
 Polyribosomes
 Liver Regeneration, 79-5562
 RNA, Messenger, 79-5562

Digestive System Neoplasms
 Age Factors

Digestive System Neoplasms (cont'd)
 Epidemiology, 79-5964
 Cervix Neoplasms
 Epidemiology, Japan, 79-5965
 Diet
 Bracken Fern, 79-5965
 Dipropylamine, 2,2'-Dihydroxy-N-nitroso-
 Carcinogenic Potential, 79-5564
 Dipropylamine, 2,2'-Dioxo-N-nitroso-
 Carcinogenic Potential, 79-5564
 Ethyl Alcohol
 Smoking, 79-5965
 Gastrointestinal Diseases
 Epidemiology, France, 79-5966

9,10-Dimethyl-1,2-benzanthracene
 see Benz(a)anthracene, 7,12-Dimethyl-

Dimethylamine, N-Nitroso-
 Antipyrine, 4-(Dimethylamino)-
 Drug Contamination, 79-5546
 Chromosome Aberrations
 Lymphocytes, 79-5575
 DNA
 Strand Breaks, Liver, 79-5559
 DNA Repair
 Spermatids, Mouse, 79-5565
 Food Contamination
 Carcinogenic Potential, Review
 79-5412
 Microsomes, Liver
 Proteins, 79-5517
 Occupational Hazard
 Herbicides, Review, 79-5413

Diphenol Oxidases
 Melanocytes
 Aging, 79-5992

Dipine
 see Phosphine Oxide, 1,4-Piperazinediylbis(bis(1-aziridinyl))-

Dipropylamine, 2,2'-Dihydroxy-N-nitroso-
 Digestive System Neoplasms
 Carcinogenic Potential, 79-5564
 Esophageal Neoplasms
 Histological Study, Rat, 79-5564
 Respiratory Tract Neoplasms
 Carcinogenic Potential, 79-5564

Dipropylamine, 2,2'-Dioxo-N-nitroso-
 Digestive System Neoplasms
 Carcinogenic Potential, 79-5564
 Respiratory Tract Neoplasms
 Carcinogenic Potential, 79-5564
 Thyroid Neoplasms
 Histological Study, Rat, 79-5564
 Urogenital Neoplasms
 Carcinoma, Epidermoid, 79-5564
 Histological Study, Rat, 79-5564

Dipropylamine, N-Nitroso-
 Occupational Hazard
 Herbicides, Review, 79-5413

Disgerminoma
 Testicular Neoplasms
 Acetophenone, 2-Amino-, 79-5673

Disulfide, Bis(diethylthiocarbamoyl)-
 Bladder Neoplasms
 1-Butanol, 4-(Butylnitrosamino)-
 79-5558

Dithiothreitol
 see 2,3-Butanediol, 1,4-Dimercapto-

Diverticulosis
 Esophageal Neoplasms
 Carcinoma, Epidermoid, 79-5895
 Case Report, 79-5895
 Pharyngeal Neoplasms
 Carcinoma, Epidermoid, 79-5895

DNA
 Apurinic Endonuclease
 Enzymatic Activity, 79-5628
 Brain Neoplasms
 Cell Cycle Kinetics, 79-5995

- DNA (cont'd)**
 Flow Cytometry, 79-5995
 Dimethylamine, *N*-Nitroso-
 Strand Breaks, Liver, 79-5559
 Extrachromosomal Inheritance
 RNA, Messenger, 79-5716
 Granuloma
 Alkaline Elution Assay, 79-5577
 Cyclophosphamide, 79-5577
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-5577
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Strand Breaks, Liver, 79-5559
 Gynecologic Neoplasms
 Adenocarcinoma, 79-5996
 Cystadenocarcinoma, 79-5996
 Nucleoproteins, 79-5996
 Hepatoma
 Virus, Avian Leukosis, 79-5700
 Mutagens
 Bioassays, Review, 79-5424
 Platinum, Diamminedichloro-, *cis*-
 Alkaline Elution Assay, 79-5542
 Urea, Ethyl Nitroso-
 Hydrogen Bonding, 79-5568
- DNA, Circular**
 Virus, Herpes Papio
 B-Lymphocytes, 79-5768
- DNA, Neoplasm**
 Leukemia, Myelocytic
 DNA-RNA Hybridization, 79-5982
 Nucleotide Sequence, 79-5982
 Virus, Rous Sarcoma
 Nucleotide Sequence, 79-5711
- DNA Nucleotidyltransferases**
 Fibrosarcoma
 T-Lymphocytes, 79-5833
- DNA Photolase**
 Radiation, Ionizing
 Caffeine, 79-5688
 Ultraviolet Rays
 Caffeine, 79-5688
- DNA Polymerase**
 Plasmacytoma
 Manganese, 79-5986
 Thymine Nucleotides, 79-5986
 Virus, Herpes Simplex 1
 Exonuclease, 79-5771
 Isolation and Characterization
 79-5771
 Peptides, 79-5771
- DNA Repair**
 Acetamide, *N*-(Acetyloxy)-*N*-fluorenyl-
 Mutagenic Activity, 79-5617
 Biphenylidol, 4-Amino-
 Mutagenic Activity, 79-5617
 Diethylamine, 2,2'-Dichloro-*N*-methyl-
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 79-5586
 Dimethylamine, *N*-Nitroso-
 Spermatids, Mouse, 79-5565
Escherichia coli
 Enzyme Induction, 79-5579
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Chloramphenicol, 79-5589
 Enzyme Induction, 79-5579
 Purine, 2-Amino-6-methoxy-, 79-5579
 Methanesulfonic Acid, Methyl Ester
 Endonucleases, 79-5628
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 79-5586
 2-Naphthylamine
 Mutagenic Activity, 79-5617
 Purine, 2-Amino-6-methoxy-
 Enzyme Induction, 79-5579
 Radiation, Ionizing
 2,3-Butanediol, 1,4-Dimercapto-
 79-5688
 Skin Diseases
 Genetics, 79-5692
p-Toluidine, *N*-Isopropyl- α -(2-
 methylhydrazino)-
- DNA Repair (cont'd)**
 Arabinose Resistance, 79-5606
 Ultraviolet Rays
 Endonucleases, 79-5628
 Urea, Methyl Nitroso-
 Adenine, 3-Methyl-, 79-5567
 Guanine, 7-Methyl-, 79-5567
 Hamster V79 Cells, 79-5567
 Purine, 2-Amino-6-methoxy-, 79-5567
 79-5579
 Spermatids, Mouse, 79-5565
 Virus, SV40
 Xeroderma Pigmentosum, 79-5797
- DNA Replication**
 Aflatoxin B1
 Precancerous Conditions, 79-5619
 Benzo(a)pyrene-1,6-dione
 Cytotoxicity, 79-5656
 Benzo(a)pyrene-3,6-dione
 Cytotoxicity, 79-5656
 Bladder Neoplasms
 Phosphine Sulfide, Tris(1-aziridinyl)-
 79-5539
 Hepatoma
 Diethylamine, *N*-Nitroso-, 79-5561
 Precancerous Conditions, 79-5561
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 Half-Wave Reduction Potential
 79-5585
 L Cells
 Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-
 furyl)-, 79-5585
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 79-5585
 Virus, Adeno 2 - SV40 Hybrid
 Clone Cells, 79-5810
 Virus, Moloney Murine Leukemia
 RNA, Transfer, 79-5752
 RNA, Viral, 79-5752
 Virus, Polyoma
 RNA, Messenger, 79-5786
 Water, Heavy
 Bone Marrow, Lymphoid Tissue
 79-5676
- DNA Restriction Enzyme**
 Virus, Simian Adeno 38
 Cleavage Sites, 79-5767
- DNA, Single Stranded**
 Virus, SV40
 Cell Transformation, Neoplastic
 79-5798
 DNA-RNA Hybridization, 79-5798
- DNA, Superhelical**
 Virus, Avian Myeloblastosis
 Endonucleases, 79-5705
- DNA, Viral**
 Burkitt's Lymphoma
 Virus, Epstein-Barr, 79-5780, 79-5781
 79-5782
 Hepatoma
 Virus, Hepatitis, 79-5457
 Infectious Mononucleosis
 Virus, Epstein-Barr, 79-5780
 Lymphoma
 Virus, Marek's Disease Herpes
 79-5722
 Nasopharyngeal Neoplasms
 Virus, Epstein-Barr, 79-5780
 Neoplasms, Experimental
 Virus, Adeno 7, 79-5817
 Virus, Adeno 2
 Carrier Proteins, 79-5809
 Deletion Mutants, 79-5810
 Mutation, 79-5809
 Virus, Helper, 79-5810
 Virus, Adeno 5
 Carrier Proteins, 79-5809
 Mutation, 79-5809
 Virus, Adeno 7
 Cleavage Sites, 79-5816
 Endonucleases, 79-5816
 Virus, Adeno 12
 Morphological Revertants, 79-5818
- DNA, Viral (cont'd)**
 Virus, Avian Leukosis
 Crosses, Genetic, 79-5699
 Virus, Avian Sarcoma
 Viral Interference, 79-5710
 Virus, Epstein-Barr
 Cleavage Sites, 79-5780
 Endonucleases, 79-5780
 Lymphocyte Transformation, 79-5779
 Nucleotide Sequence, 79-5779
 RNA, Messenger, 79-5779
 Virus, Feline Leukemia
 Nucleotide Sequence, 79-5758
 Virus, Feline Sarcoma
 Nucleotide Sequence, 79-5758
 Virus, Herpes Papio
 Nucleic Acid Hybridization, 79-5768
 Virus, Herpes Simplex 1
 RNA, Messenger, 79-5770
 Virus, Herpes Simplex 2
 Cell Transformation, Neoplastic
 79-5773
 Fibroblasts, Hamster, 79-5773
 Virus, Influenza
 Thymine, 5,6-Dihydro-6-hydroperoxy-
 5-hydroxy-, 79-5581
 Uracil, 5-Hydroperoxymethyl-
 79-5581
 Virus, Kirsten Murine Leukemia
 Reverse Transcriptase, 79-5750
 Virus, Kirsten Murine Sarcoma
 Cell Transformation, Neoplastic
 79-5745
 Phenotypic Reversion, 79-5745
 Reverse Transcriptase, 79-5750
 Virus, Moloney Murine Leukemia
 Reverse Transcriptase, 79-5750
 Virus, Polyoma
 Antigens, Neoplasm, 79-5786
 Nucleotide Sequence, 79-5786
 Virus, Polyoma, BK
 Nucleotide Sequence, 79-5788
 Virus, Polyoma, JC
 Nucleotide Sequence, 79-5788
 Virus, Rauscher Murine Leukemia
 Reverse Transcriptase, 79-5750
 Virus, Rous Sarcoma
 Cell Transformation, Neoplastic
 79-5709
 DNA-RNA Hybridization, 79-5713
 NIH/3T3 Cells, 79-5708
 Transformation, Genetic, 79-5708
 Ultraviolet Rays, 79-5713
 Virus, Simian Adeno 7
 Methanesulfonic Acid, Methyl Ester
 79-5640
 Sulfuric Acid, Nickel Salt, 79-5640
 Virus, Simian Adeno 38
 Physicochemical Properties, 79-5767
 Virus, SV40
 Antigens, Neoplasm, 79-5792
 Chromatin, 79-5794
 Deletion Mutants, 79-5793
 Depurination, 79-5797
 Methanesulfonic Acid, Methyl Ester
 79-5797
 Nuclear Morphology, 79-5792
 Nucleotide Sequence, 79-5788
 RNA, Messenger, 79-5793
 RNA Polymerase, 79-5794, 79-5795
 Temperature Sensitive Mutants
 79-5800
 Transformation, Genetic, 79-5799
 79-5800
- DOPA Oxidase**
 Melanoma
 Transplantation, Heterologous
 79-5879
 Ultrastructural Study, 79-5879
- Down's Syndrome**
 Mitomycin C
 Chromosome Aberrations, 79-5675
 Radiation, Ionizing
 Chromosome Aberrations, 79-5675
 79-5851

Drosophila melanogaster

- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-
Mutagenic Activity, 79-5524

Drug Therapy

- Leukemia, Lymphoblastic
Chromosome Aberrations, 79-5513
Leukemia, Myeloblastic
Chromosome Aberrations, 79-5513
Leukemia, Myelocytic
Chromosome Aberrations, 79-5513
Lupus Erythematosus, Discoid
Benzenecetic Acid, α -Methyl-4-(2-methylpropyl)-, 79-5884
Trophoblastic Tumor
Chromosome Aberrations, 79-5512

Drug Therapy, Combination

- Leukemia, Monocytic
Hodgkin's Disease, 79-5866

Drugs

- Animal Diseases
Food Contamination, Review, 79-5427
Barbituric Acid, 5-Ethyl-5-phenyl-
Carcinogenic Potential, Review
79-5402
Carcinogen, Chemical
Animal Feed, Review, 79-5427
Liver Diseases
Epidemiology, Review, 79-5436
Liver Neoplasms
Precancerous Conditions, Review
79-5436

Duodenal Neoplasms

- Leiomyosarcoma
Case Report, 79-5901

Duodenal Ulcer

- Neurilemmoma
Precancerous Conditions, 79-5900

Dwarfism

- Radiation, Ionizing
Chromosome Aberrations, 79-5851

Dyes

- Food Additives
Risk Evaluation, Review, 79-5429

Dysgammaglobulinemia

- Stomach Neoplasms
Case Report, 79-5842

5,8,11,14-Eicosatetraenoic Acid

- Melittin
Metabolism, Fibroblasts, 79-5624
12-*O*-Tetradecanoylphorbol-13-acetate
Metabolism, Fibroblasts, 79-5624

Ellipticine

- Mutagens
Ames Test, 79-5646

Ellipticine, 9-Fluoro-

- Mutagens
Ames Test, 79-5646

Ellipticine, 9-Hydroxy-

- Aflatoxin B1
Ames Test, 79-5646
Benzo(a)pyrene
Ames Test, 79-5646
Cholanthrene, 3-Methyl-
Ames Test, 79-5646
Ethidium Bromide
Ames Test, 79-5646

Endonucleases

- Acetamide, *N*-Fluorenyl-2-yl-
Ultraviolet Rays, 79-5628
Benz(a)anthracene, 7,12-Dimethyl-
Cell Transformation, Neoplastic
79-5628
Methanesulfonic Acid, Methyl Ester
DNA Repair, 79-5628
Ultraviolet Rays
DNA Repair, 79-5628
Virus, Adeno 7
DNA, Viral, 79-5816

Endonucleases (cont'd)

- Virus, Avian Myeloblastosis
DNA, Superhelical, 79-5705
Reverse Transcriptase, 79-5705
Virus, Epstein-Barr
DNA, Viral, 79-5780

Endotoxins

- Macrophages
Activation, Review, 79-5461

Endrin

- Adrenal Gland Neoplasms
Carcinogenic Potential, Review
79-5434
Carcinogenic Activity
Rat, Mouse, Review, 79-5434
Gynecologic Neoplasms
Carcinogenic Potential, Review
79-5434
Mammary Neoplasms, Experimental
Carcinogenic Potential, Review
79-5434
Pituitary Neoplasms
Carcinogenic Potential, Review
79-5434
Thyroid Neoplasms
Dog, Review, 79-5434

Environmental Hazard

- Bladder Neoplasms
Epidemiology, France, 79-5970
Carcinogen, Chemical
Risk Evaluation, Review, 79-5429
Ethanol, *N*-Nitrosoimino-
Carcinogenic Potential, Review
79-5413
Mutagens
Risk Evaluation, Review, 79-5429
Nitrosamines
Carcinogenic Potential, Review
79-5410, 79-5413

Enzymes

- Hepatoma
Metabolism, Review, 79-5466
Leukemia, Myelocytic
Erythrocytes, 79-5855

Eosinophils

- Leukemia, Myelocytic
Sarcoma, Reticulum Cell, 79-5856

Ependymoma

- Brain Neoplasms
Virus, Polyoma, BK, 79-5791

Epidermal Growth Factors

- see Peptides

Epoxide Hydratases

- Benzene, (Epoxethyl)-
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-5604
Benzo(a)pyrene 4,5-Oxide
Liver, Rat, 79-5652
Cholanthrene, 3-Methyl-
Microsomes, Liver, 79-5609
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Microsomes, 79-5604
Styrene
Microsomes, Liver, 79-5609

Ergocryptine, 2-Bromo-

- Adenoma
Somatotropin, 79-5595
Mammary Neoplasms, Experimental
Prolactin, 79-5997

Erythrocytes

- Glucose, 2-Deoxy-
Adenosine Triphosphate, 79-5977
Leukemia, Myelocytic
Enzymes, 79-5855
Tubercidin
Adenosine Triphosphate, 79-5977
Lactic Acid, 79-5977

Erythroleukemia

- Virus, Friend Murine Leukemia

Erythroleukemia (cont'd)

- Immune Serums, 79-5742

Erythropoietin

- Adenocarcinoma
Polycythemia, 79-5914
Kidney Neoplasms
Adenocarcinoma, 79-5914
Neoplasm Metastasis, 79-5914

Escherichia coli

- Carcinogen, Chemical
Mutation, Review, 79-5424
DNA Repair
Enzyme Induction, 79-5579
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Purine, 2-Amino-6-methoxy-, 79-5589
Nitrous Acid, Sodium Salt
Mutation, 79-5557
Radiation, Ionizing
Caffeine, 79-5688

Esophageal Neoplasms

- Adenocarcinoma
Epidemiology, Nigeria, 79-5961
Esophagitis, Peptic, 79-5897
Carcinoma, Epidermoid
Diverticulosis, 79-5895
Epidemiology, France, 79-5967
Epidemiology, Nigeria, 79-5961
Esophagitis, Peptic, 79-5897
Scleroderma, Systemic, 79-5894
Carcinoma In Situ
Esophagitis, Peptic, 79-5897
Dipropylamine, 2,2'-Dihydroxy-*N*-
nitroso-
Histological Study, Rat, 79-5564
Diverticulosis
Case Report, 79-5895
Esophagitis, Peptic
Case Report, 79-5897
Nicotine, 1'-Demethyl-1'-nitroso-
Tobacco Alkaloids, Review, 79-5414
Papilloma
Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
1-nitroso-, 79-5571
Urea, 1-(2-Chloroethyl)-3,3-dimethyl-
1-nitroso-, 79-5571
Scleroderma, Systemic
Case Report, 79-5894
Surgery, Plastic
Case Report, 79-5898

Esophageal Stenosis

- Surgery, Plastic
Case Report, 79-5898

Esophagitis, Peptic

- Esophageal Neoplasms
Adenocarcinoma, 79-5897
Carcinoma, Epidermoid, 79-5897
Carcinoma In Situ, 79-5897
Case Report, 79-5897

Estradiol

- Breast Neoplasms
Receptors, Hormone, 79-5637
Lymphocytes
Concanavalin A, 79-5670
Lipopolysaccharides, 79-5670
Mammary Neoplasms, Experimental
Receptors, Hormone, 79-5637
Receptors, Hormone
Estrogen Agonists, Review, 79-5438
4,4'-Stilbenediol, α,α' -Diethyl-
Receptors, Hormone, 79-5637

Estradiol, 3-Benzate

- Vaginal Neoplasms
Histological Study, Mouse, 79-5669
Precancerous Conditions, 79-5669

Estradiol, 3-(Bis(2-chloroethyl)carbamate),

- Dihydrogen phosphate
Ames Test
Microsomes, Liver, 79-5574

Estradiol, 17-Ethynyl-

- Hepatoma
Contraceptives, Oral, 79-5941

- Estradiol, 17-Ethynyl- (cont'd)**
Liver Neoplasms
Diagnosis, Review, 79-5503
- Estril**
Breast Neoplasms
Pregnancy, 79-5508
Receptors, Hormone
Estrogen Agonists, Review, 79-5438
- Estrogens**
Glioma
Urea, Methyl Nitroso-, 79-5925
Gynecologic Neoplasms
Carcinogenic Potential, Review
79-5442
Uterine Neoplasms
Epidemiology, 79-5929
Epidemiology, Review, 79-5439
Menopause, 79-5929, 79-5949
- Estrone**
Mammary Neoplasms, Experimental
Carcinoma, Papillary, 79-5997
- Estrus**
Mammary Neoplasms, Experimental
Strain Differences, Mouse, 79-5665
- Ethacryl**
Connective Tissue
Cell Transformation, Neoplastic
79-5677
- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-**
Drosophila melanogaster
Mutagenic Activity, 79-5524
Hepatoma
Carcinogenic Potential, Mouse
79-5525
- Ethane, 1,2-Dibromo-**
Spermatozoa
Abnormalities, 79-5521
Chromatin, 79-5521
Teratogenic Effect, 79-5522
- Ethane, 1,1,1-Trichloro-**
Chick Embryo
Teratogenic Effect, 79-5523
- Ethane, 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)-**
Ames Test
Mutagenic Metabolite, 79-5526
Pesticides
Carcinogenic Potential, Review
79-5402
- Ethanol, 1,1-Bis(p-chlorophenyl)-2,2,2-trichloro-**
Ames Test
Mutagenic Metabolite, 79-5526
- Ethanol, N-Nitrosoiminodi-**
Environmental Hazard
Carcinogenic Potential, Review
79-5413
Occupational Hazard
Carcinogenic Potential, Review
79-5413
- Ethanol, 2-(2,4,5-Trichlorophenoxy)-**
Aryl Hydrocarbon Hydroxylases
Microsomes, Liver, 79-5519
Hepatoma
Dose-Response Study, Mouse, 79-5520
Liver Neoplasms
Dose-Response Study, Mouse, 79-5519
- Ethidium Bromide**
7,8-Benzoflavone
Ames Test, 79-5646
Ellipticine, 9-Hydroxy-
Ames Test, 79-5646
Virus, Rous Sarcoma
Cytochrome Oxidase, 79-5714
- Ethyl Alcohol**
Aryl Hydrocarbon Hydroxylases
Microsomes, Liver, 79-5518
Cytochrome P-450
- Ethyl Alcohol (cont'd)**
Microsomes, Liver, 79-5518
Digestive System Neoplasms
Smoking, 79-5965
Hepatoma
Epidemiology, 79-5959
Laryngeal Neoplasms
Epidemiology, 79-5888
Smoking, 79-5889
Liver Neoplasms
Epidemiology, Review, 79-5502
NADPH Cytochrome C Reductase
Microsomes, Liver, 79-5518
Pyrrolidine, 1-Nitroso-
Metabolism, 79-5578
- Ethylene**
Mutagenic Activity
Dose-Response Study, Review
79-5445
- Ethylene, 1,1-Bis(p-chlorophenyl)-**
Microsomes, Liver
Mutagenic Metabolite, 79-5526
- Ethylene, Chloro-**
Angiosarcoma
Dose-Response Study, Rat, 79-5527
Epidemiology, Review, 79-5436
Mathematical Model, 79-5527
Transplacental Carcinogenesis, Review
79-5437
Chromosome Aberrations
Lymphocytes, 79-5575
Drug Packaging
Carcinogenic Potential, Review
79-5403
Liver Neoplasms
Adenosine Triphosphatase, 79-5528
Precancerous Conditions, 79-5528
Microsomes, Liver
RNA, Binding, 79-5528
- Ethylene, 1,1-Dichloro-2,2-bis(p-chlorophenyl)-**
Cholinesterases
Plasma Enzymes, 79-5529
Iditol Dehydrogenase
Plasma Enzymes, 79-5529
- Ethylene Oxide, 1,1-Bis(p-chlorophenyl)-**
Pyridine, 4-(p-Nitrobenzyl)-
Alkylating Activity, 79-5526
- Ethylene, Tetrachloro-**
Chick Embryo
Teratogenic Effect, 79-5523
- Ethylene, Trichloro-**
Carcinogenic Metabolite
Species Difference, Review, 79-5401
Chick Embryo
Teratogenic Effect, 79-5523
Liver Neoplasms
Precancerous Conditions, 79-5528
Microsomes, Liver
RNA, Binding, 79-5528
Occupational Hazard
Epidemiology, Review, 79-5401
- Ethylenimine**
Chromosome Aberrations
Lymphocytes, 79-5530
- Exonuclease**
Virus, Herpes Simplex 1
DNA Polymerase, 79-5771
- Extrachromosomal Inheritance**
Agrobacterium tumefaciens
Recombination Defective Mutants
79-5576
DNA
RNA, Messenger, 79-5716
Plant Tumors
Agrobacterium tumefaciens, 79-5981
Procollagen
RNA, Messenger, 79-5716
- Eye Neoplasms**
Carcinoma, Epidermoid
Case Report, 79-5876
Classification, Review, 79-5477
Choriocarcinoma
Neoplasm Metastasis, 79-5920
Leukoplakia
Classification, Review, 79-5477
Melanoma
Case Report, 79-5875
Classification, Review, 79-5477
Glaucoma, 79-5875
Melanosis, 79-5877
Melanosis
Case Report, 79-5877
Phosphorus Radioisotopes
Diagnosis, 79-5985
Surgery, Operative
Neoplasm Recurrence, Local, 79-5875
- Factor IX**
Virus, Herpes Simplex
Genetics, 79-5769
- Fibroblasts**
Virus, Abelson Murine Leukemia
Reverse Transcriptase, 79-5737
Virus, Harvey Murine Sarcoma
Cell Transformation Neoplastic
79-5749
Virus, Kirsten Murine Sarcoma
Cell Transformation Neoplastic
79-5749
Virus, Rat Sarcoma
Cell Transformation Neoplastic
79-5749
Xeroderma Pigmentosum
Pyrimidine Nucleotides, 79-5993
- Fibrosarcoma**
Bone Neoplasms
Radiation, Ionizing, 79-5449
Cholanthrene, 3-Methyl-
Immune Response, Rat, 79-5639
Immunity, Cellular, 79-5834
T-Lymphocytes
Antigens, Neoplasm, 79-5834
DNA Nucleotidyltransferases, 79-5833
Growth, 79-5833
Histocompatibility Antigens, 79-5834
Immunity, Passive, 79-5833
Plasmacytoma
Hybrid Cells, 79-5831
Ultraviolet Rays
Immunity, Cellular, 79-5834
Virus, Herpes Simplex 2
Karyotyping, 79-5775
Nucleic Acids, 79-5775
Peptides, 79-5775
- Fluocinolone Acetonide**
Skin Neoplasms
12-O-Tetradecanoylphorbol-13-acetate
79-5633
- Fluoren-2-amine**
5,6-Benzoflavone
Metabolism, Liver, 79-5551
- Fluoride**
Plutonium
Inhalation Study, Dog, 79-5682
- Fluorosulfuric Acid, Methyl Ester**
Toxicity
Administration Route, 79-5545
Inhalation Study, Rat, 79-5545
- Food Additives**
Amaranth
Carcinogenic Potential, Review
79-5402
Dyes
Risk Evaluation, Review, 79-5429
2-Naphthylamine
Carcinogenic Potential, Review
79-5403
- Food Contamination**
Diethylamine, N-Nitroso-

Food Contamination (cont'd)
 Carcinogenic Potential, Review
 79-5412

Dimethylamine, *N*-Nitroso-
 Carcinogenic Potential, Review
 79-5412

Hepatoma
 Epidemiology, Tanzania, 79-5960

Jaundice
 Toxins, 79-5960

Methemoglobinemia
 Nitric Acid, 79-5926

Mycotoxins
 Epidemiology, Review, 79-5428

Nitric Acid
 Fertilizers, 79-5926

Nitrosamines
 Quantitation Method, Review, 79-5411

Pyrolidine, 1-Nitroso-
 Carcinogenic Potential, Review
 79-5412

Radioactive Fallout
 Greenland, 79-5927

Formaldehyde
 Mutagenic Activity
 Dose-Response Study, Review
 79-5445

Formamide, *N,N*-Dimethyl-
 Colonic Neoplasms
 Cell Differentiation, 79-5999

Mammary Neoplasms, Experimental
 Cell Differentiation, 79-5999

Rhabdomyosarcoma
 Cell Differentiation, 79-5999

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 Bladder Neoplasms
 Phosphine Sulfide, Tris(1-aziridinyl)-
 79-5539

Formic Acid, 1-Methyl Hydrazide
 Hepatoma
 Mushroom Mycotoxin, 79-5549

Fotrin
 Chromosome Aberrations
 Lymphocytes, 79-5530

Fucose
 Adenocarcinoma
 Membrane Proteins, 79-6000

Furan, 2-(*N*-Ethylcarbamoyloxymethyl)-
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Carcinogenic Metabolite, 79-5618

Glutathione
 DNA, Binding, 79-5618

Microsomes, Liver
 Carcinogenic Metabolite, 79-5618

Gallic Acid, Propyl Ester
 Chromosome Aberrations
 Plants, 79-5603

Radiation, Ionizing
 Chromosome Aberrations, 79-5603

Gastrectomy
 Stomach Neoplasms
 Diagnosis, Review, 79-5488

Epidemiology, Review, 79-5484
 Precancerous Conditions, 79-5488

Gastric Mucosa
 Gastritis
 Immunoglobulins, 79-5841

Metaplasia
 Immunoglobulins, 79-5841

Stomach Neoplasms
 Immunoglobulins, 79-5841

Gastritis
 Gastric Mucosa
 Immunoglobulins, 79-5841

Stomach Neoplasms
 Epidemiology, Japan, 79-5504

Precancerous Conditions, Review
 79-5484

Gastrointestinal Diseases
 Digestive System Neoplasms
 Epidemiology, France, 79-5966

Gastrointestinal Neoplasms
 Acetic Acid, Methylnitrosaminomethyl
 Ester
 Administration Route, Rat, 79-5550

Adenocarcinoma
 Epidemiology, France, 79-5967

Adenomatosis, Familial Endocrine
 Peptides, Review, 79-5483

Neoplastic Endocrine-Like Syndromes
 Glucagon, 79-5483

Insulin, 79-5483
 Peptides, Review, 79-5483

Somatotropin Release Inhibiting Hor-
 mone, 79-5483

Plasmacytoma
 Immunosuppression, 79-5908

Transplantation, 79-5908

Genetics
 Bladder Neoplasms
 Carcinoma, Transitional Cell, 79-5910

Brain Neoplasms
 Case Report, 79-5873

Breast Neoplasms
 Tumor Laterality, 79-5947

Carcinogen, Chemical
 Risk Factors, Review, 79-5474

Carcinoma, Transitional Cell
 Case Report, 79-5910

Hodgkin's Disease
 Case Report, 79-5854, 79-5867

Histocompatibility Antigens, 79-5867

Hypercholesteremia
 Animal Model, Mouse, 79-5988

Intestinal Neoplasms
 Adenoma, 79-5902

Laryngeal Neoplasms
 Carcinoma, Epidermoid, 79-5888

Melanoma
 Case Report, 79-5881

Mycosis Fungoides
 Epidemiology, 79-5933

Oncogenic Viruses
 Risk Factors, Review, 79-5474

Ovarian Neoplasms
 Blood Groups, 79-5955

Epidemiology, 79-5955
 Radiation, Ionizing
 Dose-Response Study, 79-5689

Risk Factors, Review, 79-5474

Rectal Neoplasms
 Adenocarcinoma, 79-5899

Case Report, 79-5899

Sarcoma, Reticulum Cell
 Case Report, 79-5854

Skin Diseases
 DNA Repair, 79-5692

Spermatozoa
 Abnormalities, Review, 79-5421

Stomach Neoplasms
 Case Report, 79-5899

Virus, AKR Murine Leukemia
 Immune Response, Review, 79-5455

Virus, Friend Murine Leukemia
 Immune Response, 79-5743

Immune Response, Review, 79-5455

Virus, Herpes Simplex
 Complement, 79-5769

Factor IX, 79-5769

Virus, Murine Mammary Tumor
 Transmission, Review, 79-5458

Giant Cell Tumors
 Bone Neoplasms
 Ultrastructural Study, 79-5886

Glaucoma
 Eye Neoplasms
 Melanoma, 79-5875

Glioblastoma Multiforme
 Brain Neoplasms
 Intestinal Polyps, 79-5873

Glioma
 Alanine
 Peptide Synthesis, 79-5980

Brain Neoplasms
 Urea, Methyl Nitroso-, 79-5566

Butyric Acid, 4-Amino-
 Peptide Synthesis, 79-5980

Histidine, *N*- β -Alanyl-
 Isolation and Characterization
 79-5980

Ornithine
 Peptide Synthesis, 79-5980

Tissue Culture
 Ultrastructural Study, 79-5566

Urea, Methyl Nitroso-
 Estrogens, 79-5925

Ultrastructural Study, 79-5925

Glucagon
 Gastrointestinal Neoplasms
 Neoplastic Endocrine-Like Syndromes
 79-5483

Hepatoma
 Tyrosine Aminotransferase, 79-5704

Glucocorticoids
 Leukemia, Myelocytic
 Immune Response, Mouse, 79-5824

Glucosamine
 Colonic Neoplasms
 Membrane Proteins, 79-6000

Glucose Dehydrogenases
 Leukemia, Myeloblastic
 Granulocytes, 79-5859

Isoenzymes, 79-5859
 Monocytes, 79-5859

Glucose, 2-Deoxy-
 Adenosine Triphosphate
 Erythrocytes, 79-5977

Glucosephosphate Dehydrogenase
 Hepatoma
 Virus, Avian Leukosis, 79-5703

Glucuronidase
 Benzo(a)pyrene
 Phenol Metabolites, 79-5651

Benzo(a)pyrene, 7,8-Dihydro-7,8-
 dihydroxy-
 Carcinogenic Metabolite, 79-5651

Benzo(a)pyrene, 9,10-Dihydro-9,10-
 dihydroxy-
 Carcinogenic Metabolite, 79-5651

Laryngeal Neoplasms
 Neutrophils, 79-5844

Glutathione
 Aflatoxin B1
 DNA, Binding, 79-5618

Furan, 2-(*N*-Ethylcarbamoyloxymethyl)-
 DNA, Binding, 79-5618

Quinoline, 4-Nitro-, 1-Oxide
 Toxicity, 79-5592

Glutathione Peroxidase
 Selenium
 Antineoplastic Activity, Review
 79-5405

Glutathione Transferases
 Benzene, 1,2-Dichloro-4-nitro-
 Phenol, (1,1-Dimethylethyl)-4-
 methoxy-, 79-5604

Benzo(a)pyrene 4,5-Oxide
 Liver, Rat, 79-5652

Phenol, (1,1-Dimethylethyl)-4-methoxy-
 Cytosol, 79-5604

Glycopeptides
 Virus, AKR Murine Leukemia
 Isolation and Characterization
 79-5755

Virus, Rauscher Murine Leukemia
 Isolation and Characterization
 79-5755

Glycoproteins
 Colonic Neoplasms

- Glycoproteins (cont'd)**
 Adenocarcinoma, 79-6000
 Concanavalin A, 79-6000
 Oligosaccharides, 79-6000
Mammary Neoplasms, Experimental
 Growth, 79-5847
 Histocompatibility Antigens, 79-5848
 Neoplasm Transplantation, 79-5847
 79-5848
Neuroblastoma
 Cell Differentiation, 79-5984
 Methane, Sulfinylbis-, 79-5984
Stomach Neoplasms
 Cimetidine, 79-5416
 Virus, Avian Myeloblastosis
 Hexoses, 79-5706
 Lactic Acid, 79-5706
 Virus, Friend Murine Leukemia
 Antibody Specificity, 79-5742
 Virus, Murine Mammary Tumor
 Antigen-Antibody Reactions, 79-5731
 Lymphocyte Transformation, 79-5731
 Virus, Rous Sarcoma
 Hexoses, 79-5706
- Gossypol**
 Ames Test
 Contraceptives, Male, 79-5674
- Graft vs Host Reaction**
 Bone Marrow
 Killer Cells, Review, 79-5460
 Lymphoma
 B-Lymphocytes, 79-5826
 T-Lymphocytes, 79-5826
- Granulocytes**
 Leukemia, Myeloblastic
 Glucose Dehydrogenases, 79-5859
- Granuloma**
 DNA
 Alkaline Elution Assay, 79-5577
 Cyclophosphamide, 79-5577
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-5577
 Stomach Neoplasms
 Polyps, 79-5896
 p-Toluidine, N-Isopropyl- α -(2-
 methylhydrazino)-
 Methanesulfonic Acid, Methyl Ester
 79-5577
- Granulosa Cell Tumor**
 Adrenal Gland Neoplasms
 Acetophenone, 2-Amino-, 79-5673
 Ovarian Neoplasms
 Acetophenone, 2-Amino-, 79-5673
- Growth**
 Carcinoma
 Neoplasm Transplantation, 79-5994
 Carcinoma 256, Walker
 Intestines, Small, 79-5691
 Colonic Neoplasms
 BCG, 79-5843
 Fibrosarcoma
 T-Lymphocytes, 79-5833
 Liver Neoplasms
 Ceruloplasmin, 79-5998
 Mammary Neoplasms, Experimental
 Ceruloplasmin, 79-5998
 Glycoproteins, 79-5847
 Melanoma
 Transplantation, Heterologous
 79-5991
 Neoplasms
 Mouse, Nude, Review, 79-5469
 Sarcoma, Mast Cell
 Electroshock, 79-5987
 Stress, 79-5987
- Guanidine, 1-Methyl-3-nitro-1-nitroso-**
Agrobacterium tumefaciens
 Recombination Defective Mutants
 79-5576
 Chloramphenicol
 DNA Repair, 79-5589
 DNA
- Guanidine, 1-Methyl-3-nitro-1-nitroso-**
 (cont'd)
 Strand Breaks, Liver, 79-5559
 DNA Repair
 Enzyme Induction, 79-5579
 Granuloma
 DNA, 79-5577
 Purine, 2-Amino-6-methoxy-
 DNA Repair, 79-5579
Escherichia coli, 79-5589
 Sarcoma, Osteogenic
 Cycloheximide, 79-5746
- Guanidine, 1-Propyl-3-nitro-1-nitroso-**
 Guanyl Cyclase
 Adriamycin, 79-5590
 Methotrexate, 79-5590
 Uracil, 5-(Bis(2-chloroethyl)amino)-
 79-5590
 Stomach Neoplasms
 Adenocarcinoma, 79-5591
 Adenoma, 79-5591
 Metaplasia, 79-5591
- Guanine, 7-Methyl-**
 Triazine, 1-Methyl-3-phenyl-
 Nucleic Acids, Alkylation, 79-5584
 Urea, Methyl Nitroso-
 DNA Repair, 79-5567
- Guanosine**
 Acetamide, N-(Acetyloxy)-N-(4-(2-
 phenylethenyl)phenyl)-
 Nucleoside Adducts, 79-5554
- Guanosine, O⁶-Methyl-2'-deoxy-**
 Nucleoside Deaminases
 Cytosol, Rat, 79-5588
 Demethylation, 79-5588
- Guanyl Cyclase**
 Antineoplastic Agents
 Uracil, 5-(Bis(2-chloroethyl)amino)-
 79-5590
 Guanidine, 1-Propyl-3-nitro-1-nitroso-
 Adriamycin, 79-5590
 Methotrexate, 79-5590
 Uracil, 5-(Bis(2-chloroethyl)amino)-
 79-5590
 Hydrazine
 Adriamycin, 79-5590
 Liver, Rat, 79-5590
 Methotrexate, 79-5590
 Uracil, 5-(Bis(2-chloroethyl)amino)-
 79-5590
- Gynecologic Neoplasms**
 Adenocarcinoma
 DNA, 79-5996
 Epidemiology, 79-5953
 Carcinoma, Epidermoid
 Epidemiology, 79-5953
 Contraceptives, Oral
 Epidemiology, Review, 79-5442
 Cystadenocarcinoma
 DNA, 79-5996
 DNA
 Nucleoproteins, 79-5996
 Endrin
 Carcinogenic Potential, Review
 79-5434
 Estrogens
 Carcinogenic Potential, Review
 79-5442
 Hair Dyes
 Carcinogenic Potential, 79-5950
 Neoplasms, Multiple Primary
 Case Report, 79-5917
 Precancerous Conditions
 Cytodiagnosis, 79-5953
 Progestational Hormones
 Carcinogenic Potential, Review
 79-5442
 4,4'-Stilbenediol, α,α' -Diethyl-
 Transplacental, Transmammary Car-
 cinogenesis, 79-5667
- Hair Dyes**
 Breast Neoplasms
- Hair Dyes (cont'd)**
 Carcinogenic Potential, 79-5950
 Gynecologic Neoplasms
 Carcinogenic Potential, 79-5950
- Halothane**
 see Ethane, 2-Bromo-2-chloro-1,1,1-
 trifluoro-
- Hamartoma**
 Lung Neoplasms
 Case Report, 79-5893
- Harman**
 Benzo(a)pyrene
 Metabolism, Lung, 79-5655
 Benzo(a)pyrene, 7,8-Dihydro-7,8-
 dihydroxy-
 Metabolism, Lung, 79-5655
 5H-Pyrido(4,3b)indole, 3-Amino-1-
 methyl-
 DNA, binding, 79-5582
- Head and Neck Neoplasms**
 Child
 Diagnosis, Review, 79-5478
 Neoplasm Metastasis
 Diagnosis, Review, 79-5478
- HeLa Cells**
 Virus, Adeno 2
 RNA, Viral, 79-5811
 Virus, Adeno 4
 Lysosomes, 79-5812
 Virus, Adeno 5
 RNA, Messenger, 79-5813, 79-5814
 Virus, Adeno 31
 Lysosomes, 79-5812
 Virus, Polio
 RNA Replicase, 79-5822
- Hemangioma**
 Virus, Cytomegalo
 Maternal-Fetal Exchange, 79-5778
- Hematologic Diseases**
 Leukemia, Myelocytic
 Pyruvate Kinase, 79-5855
 Lymphosarcoma
 Pure Red Cell Aplasia, 79-5862
- Hematopoietic Stem Cells**
 Histocompatibility Antigens
 Immune Response, Review, 79-5463
 Leukemia, Myeloblastic
 Cell Differentiation, 79-5859
 Lymphoma
 Immunity, Passive, 79-5460
 Virus, Friend Murine Leukemia
 Animal Model, Tupaia, 79-5741
 Cell Differentiation, 79-5741
 Virus, Friend Spleen Focus-Forming
 Carcinogenic Activity, Review
 79-5456
 Cell Differentiation, 79-5741
 Virus, Kirsten Murine Sarcoma
 Cell Differentiation, 79-5741
 Virus, Rauscher Murine Leukemia
 Carcinogenic Activity, Review
 79-5456
- Heme**
 Benzaldehyde, 4-Methyl-
 Lung, Rabbit, 79-5607
- Hepatitis**
 Carcinogen, Chemical
 Diagnosis, Review, 79-5426
 Liver Neoplasms
 Precancerous Conditions, Review
 79-5426
- Hepatoma**
 Acetamide, N-Fluoren-2-yl-
 Piperonyl Butoxide, 79-5553
 Precancerous Conditions, 79-5489
 Acetamide, N-Fluoren-2-yl-di-
 Growth, Review, 79-5407
 Acetanilide, 4'-(p-Fluorophenyl)-
 Growth, Review, 79-5407

Hepatoma (cont'd)

- Acetanilide, 4'-Phenyl-
Piperonyl Butoxide, 79-5553
- Adenomatoid Renal Epithelium
Case Report, Infant, 79-5916
- Aflatoxin B1
Epidemiology, Review, 79-5490
Growth, Review, 79-5407
- Alpha Fetoproteins
Carcinogen, Chemical, 79-5467
- Aniline, 2,4,6-Trimethyl-
Growth, Review, 79-5407
- Antigens
Cell Membrane, Review, 79-5467
- Breast Neoplasms
Contraceptives, Oral, 79-5440
- Carcinogen, Chemical
Antigenic Determinants, Review
79-5467
Enzymatic Activity, 79-5703
- Cervix Neoplasms
Contraceptives, Oral, 79-5440
- Chromosomes
Morris Tumor, Review, 79-5407
- Classification
Ultrastructural Study, Review, 79-5490
- Contraceptives, Oral
Carcinogenic Potential, 79-5490
Epidemiology, 79-5941, 79-5942
Epidemiology, Review, 79-5436
79-5440, 79-5441, 79-5443
Estradiol, 17-Ethynyl-, 79-5941
Mestranol, 79-5941
Precancerous Conditions, 79-5942
- Cycasin
Epidemiology, Review, 79-5490
- Cytidine Triphosphate
Metabolism, Review, 79-5466
- Dexamethasone
Binding Sites, 79-5700
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Dose-Response Study, Mouse, 79-5520
- Diethylamine, *N*-Nitroso-
DNA Replication, 79-5561
Precancerous Conditions, 79-5489
- DNA Replication
Precancerous Conditions, 79-5561
- Enzymes
Metabolism, Review, 79-5466
- Ethane, 2-Bromo-2-chloro-1,1,1-trifluoro-
Carcinogenic Potential, Mouse
79-5525
- Ethanol, 2-(2,4,5-Trichlorophenoxy)-
Dose-Response Study, Mouse, 79-5520
- Ethyl Alcohol
Epidemiology, 79-5959
- Food Contamination
Epidemiology, Tanzania, 79-5960
- Formic Acid, 1-Methyl Hydrazide
Mushroom Mycotoxin, 79-5549
- Geographic Factors
Epidemiology, Review, 79-5502
- Kidney
Abnormalities, 79-5916
- Liver Cirrhosis
Alpha Fetoproteins, 79-5959
Australia Antigen, 79-5959
Precancerous Conditions, Review
79-5491
- Lymphocytes
Transplantation Immunology, 79-5704
- Morpholine, *N*-Nitroso-
Frog, Fish, 79-5593
Precancerous Conditions, 79-5489
- Neoplasm Metastasis
Morris Tumor, Review, 79-5407
- Phosphoric Acid, 2-Chloro-1-(2,4,5-
trichlorophenyl)vinyl Dimethyl
Histological Study, Mouse, 79-5538
- Phthalamic Acid, *N*-Fluorenyl-2-yl-
Growth, Review, 79-5407
- Precancerous Conditions
Ultrastructural Study, Review, 79-5489
- Radiation, Ionizing
Case Report, Fetus, 79-5696
- 4,8-Secosenecionan-8,11,16-trione, 12-
Hydroxy-4-methyl-

Hepatoma (cont'd)

- Carcinogenic Activity, Rat, 79-5572
 - Symphytine
Plant Extracts, 79-5572
 - Thymidine Kinase
Dexamethasone, 79-5704
 - Toxins
Ground Nuts, 79-5960
 - Tyrosine Aminotransferase
Dexamethasone, 79-5704
Glucagon, 79-5704
 - Virus, Avian Leukosis
BCG, 79-5704
Chromatin, 79-5700
DNA, 79-5700
Glucosephosphate Dehydrogenase
79-5703
Histocompatibility Antigens, 79-5702
Neoplasm Transplantation, 79-5701
Thymidine Kinase, 79-5703
Transplantation Immunology, 79-5704
Ultrastructural Study, 79-5701
Xanthine Oxidase, 79-5703
 - Virus, Hepatitis
Carcinogenic Potential, 79-5490
DNA, Viral, 79-5457
Epidemiology, Review, 79-5457
Epidemiology, Tanzania, 79-5960
 - Xanthine, 3-Hydroxy-
Structure-Activity Relationship
79-5594
- ## Hereditary Diseases
- Carcinogen, Environmental
Risk Factors, Review, 79-5474
 - Chromosome Aberrations
Radiation Tolerance, Review, 79-5444
- ## Hexoses
- Virus, Avian Myeloblastosis
Glycoproteins, 79-5706
 - Virus, Rous Sarcoma
Glycoproteins, 79-5706
- ## Histidine, *N*- β -Alanil-
- Glioma
Isolation and Characterization
79-5980
- ## Histiocytoma
- Liver Neoplasms
Hydrazine, Methyl-, 79-5549
- ## Histocompatibility Antigens
- Bone Marrow
Graft vs Host Reaction, Review
79-5463
 - Fibrosarcoma
T-Lymphocytes, 79-5834
 - Hematopoietic Stem Cells
Immune Response, Review, 79-5463
 - Hepatoma
Virus, Avian Leukosis, 79-5702
 - Hodgkin's Disease
Genetics, 79-5867
 - Macrophages
Immune Response, Review, 79-5463
 - Mammary Neoplasms, Experimental
Glycoproteins, 79-5848
 - Plasmacytoma
Immunogenicity, 79-5830
 - Sarcoma
Virus, Rous Sarcoma, 79-5702
Virus, SV40, 79-5836
 - Thymus Gland
Graft vs Host Reaction, Review
79-5462
 - Virus, Feline Leukemia
Antigens, Viral, 79-5761
 - Virus, Gross Murine Leukemia
Immunity, Cellular, 79-5744
 - Virus, SV40
Immunity, Cellular, 79-5803
T-Lymphocytes, 79-5803
- ## Histones
- Virus, SV40
Chromatin, 79-5802

Hodgkin's Disease

- see also* Lymphoma
 - Amyloidosis
Immune Response, Review, 79-5481
 - Benzene
Occupational Hazard, 79-5932
 - Child
Epidemiology, Review, 79-5493
 - Genetics
Case Report, 79-5854, 79-5867
 - Histocompatibility Antigens
Genetics, 79-5867
 - Leukemia, Monocytic
Drug Therapy, Combination, 79-5866
Radiation, Ionizing, 79-5866
 - Neoplasms, Multiple Primary
Case Report, 79-5866
 - Paraproteins
Isolation and Characterization, Review
79-5464
 - Pituitary Gland
Neoplasm Circulating Cells, 79-5858
 - Virus, Epstein-Barr
Antibodies, Viral, 79-5764
 - Virus, Influenza
Antibodies, Viral, 79-5764
 - Virus, Simian Sarcoma
Antibodies, Viral, 79-5764
- ## Homologous Wasting Disease
- Virus, Murine Leukemia
Immunization, 79-5725
 - Virus, Polyoma
Interferon, 79-5787
- ## Hybrid Cells
- Chromosomes, Human
Tumorigenicity, 79-5852
 - Fibrosarcoma
Plasmacytoma, 79-5831
 - L Cells
Immunogenicity, Tumorigenicity
79-5831
 - Melanoma
Antigens, 79-5839
Chromosomes, 79-5839
Tumorigenicity, 79-5839
 - Plasmacytoma
Immunity, Passive, 79-5830
Immunogenicity, Tumorigenicity
79-5831
- ## Hydrazine
- Guanyl Cyclase
Adriamycin, 79-5590
Liver, Rat, 79-5590
Methotrexate, 79-5590
Uracil, 5-(Bis(2-chloroethyl)amino)-
79-5590
- ## Hydrazine, 1,2-Dimethyl-
- Colonic Neoplasms
Neoplasm Transplantation, 79-5843
Neoplasms, Multiple Primary, 79-5547
- ## Hydrazine, 4-Hydroxymethylphenyl-
- Angioma
Angiosarcoma, 79-5549
 - Liver Neoplasms
Angioma, 79-5549
 - Lung Neoplasms
Adenocarcinoma, 79-5549
Adenoma, 79-5549
- ## Hydrazine, Methyl-
- Liver Neoplasms
Histiocytoma, 79-5549
- ## Hydrazine, Phenethyl-
- Angiosarcoma
Case Report, 79-5548
- ## Hydrocarbons, Chlorinated
- Liver Neoplasms
Environmental Hazard, Review
79-5408
- ## Hydrolases
- Asbestos
Macrophages, 79-5533

- Hydrolases (cont'd)**
 Beryllium
 Macrophages, 79-5533
- N-Hydroxy-2-aminofluorene**
 see Hydroxylamine, *N*-Fluoren-2-yl-
- Hydroxylamine, *N*-Fluoren-2-yl-**
 Ames Test
 Mutagenic Metabolite, 79-5551
- Hypothalamus**
 Benz(a)anthracene, 7,12-Dimethyl-
 Tissue Distribution, Rat, 79-5635
- Hyperaldosteronism**
 Adrenal Gland Neoplasms
 Case Report, 79-5662
 Dexamethasone, 79-5662
- Hypercalcemia**
 Bone Neoplasms
 Neoplasm Metastasis, Review, 79-5511
 Parathyroid Hormone, 79-5511
 Prostaglandins, 79-5511
 Leukemia
 Bone Resorption, Review, 79-5511
 Lymphoma
 Bone Resorption, Review, 79-5511
 Multiple Myeloma
 Bone Resorption, Review, 79-5511
 Thyroid Neoplasms
 Neoplastic Endocrine-Like Syndromes
 79-5868
- Hypercholesterolemia**
 Genetics
 Animal Model, Mouse, 79-5988
- Hyperplasia**
 Aflatoxin B1
 Parenchymal Cells, Liver, 79-5619
 Angiosarcoma
 Precancerous Conditions, Review
 79-5491
 Benzo(a)pyrene
 2-Butanone, 79-5654
 Croton Oil, 79-5654
 Toluene, 79-5654
 Bladder Neoplasms
 1-Butanol, 4-(Butylnitrosamino)-
 79-5643
 Breast Neoplasms
 Epidemiology, Review, 79-5507
 Precancerous Conditions, Review
 79-5507
 Liver Neoplasms
 Contraceptives, Oral, 79-5443
 Mammary Neoplasms, Experimental
 Fetal Mesenchyma, 79-5732
 Virus, Murine Mammary Tumor
 79-5732
 Mouth Neoplasms
 Retinol Palmitate, 79-5535
- Hypersensitivity**
 Mycosis Fungoides
 Ultraviolet Rays, 79-5933
- Hypersensitivity, Delayed**
 Breast Neoplasms
 Benzene, 1-Chloro-2,4-dinitro-
 79-5849
 Tuberculin, 79-5849
 Neoplasm Metastasis, 79-5838
 Neoplasms
 Tuberculin, 79-5838
- Iditol Dehydrogenase**
 Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 Plasma Enzymes, 79-5529
- IgA**
 Laryngeal Neoplasms
 Serum Levels, 79-5844
 Plasmacytoma
 Virus-Like Particles, 79-5820
 Stomach Neoplasms
 Secretory Component, 79-5841
- IgG**
 Pyoderma Gangrenosum
 Paraproteinemia, 79-5840
- IgM**
 Leukemia, Myelocytic
 B-Lymphocytes, 79-5827
- Imidazole-1-ethanol, 2-Methyl-5-nitro-**
 Chromosome Aberrations
 Lymphocytes, 79-5586, 79-5587
 Urinary Metabolite, 79-5586
 Diethylamine, 2,2'-Dichloro-*N*-methyl-
 DNA Repair, 79-5586
 DNA Replication
 Half-Wave Reduction Potential
 79-5585
 L Cells
 DNA Replication, 79-5585
 Methanesulfonic Acid, Methyl Ester
 DNA Repair, 79-5586
 Virus, Kirsten Murine Sarcoma
 Virus Activation, 79-5747
- Immune Serums**
 Erythrocytotoxicity
 Virus, Friend Murine Leukemia
 79-5742
 Prolactin
 Radioimmunoassay, 79-5663
 Virus, Baboon
 Neutralization, 79-5764
 Virus, Bovine Papilloma
 Cytopathogenic Effect, Viral, 79-5762
- Immunity, Cellular**
 Breast Neoplasms
 Carcinoma, 79-5849
 Precancerous Conditions, 79-5849
 Cervix Neoplasms
 Carcinoma, 79-5850
 Precancerous Conditions, 79-5850
 Colonic Neoplasms
 Surgery, Operative, 79-5547
 Fibrosarcoma
 Cholanthrene, 3-Methyl-, 79-5834
 Ultraviolet Rays, 79-5834
 Leukemia
 Killer Cells, Review, 79-5460
 Lung Neoplasms
 Adenocarcinoma, 79-5845
 Carcinoma, 79-5845
 Carcinoma, Epidermoid, 79-5845
 Mammary Neoplasms, Experimental
 Virus, Murine Mammary Tumor
 79-5731
 Melanoma
 Lymphocytes, 79-5991
 Plant Agglutinins
 Reaction, Cutaneous, 79-5845
 Tuberculin
 Reaction, Cutaneous, 79-5845
 Virus, AKR Murine Leukemia
 Antigens, Viral, 79-5744
 Virus, Avian Leukosis
 T-Lymphocytes, 79-5825
 Virus, Avian Myeloblastosis
 T-Lymphocytes, 79-5825
 Virus, Feline Sarcoma
 Lymph Nodes, 79-5837
 Virus, Gross Murine Leukemia
 Antigens, Viral, 79-5744
 Histocompatibility Antigens, 79-5744
 Virus, Rous Sarcoma
 T-Lymphocytes, 79-5825
 Virus, SV40
 Histocompatibility Antigens, 79-5803
- Immunity, Passive**
 Fibrosarcoma
 T-Lymphocytes, 79-5833
 T-Lymphocytes
 Cortisone Acetate, 79-5833
 Lymphoma
 Hematopoietic Stem Cells, 79-5460
 Plasmacytoma
 Hybrid Cells, 79-5830
 T-Lymphocytes, 79-5830
- Immunity, Passive (cont'd)**
 Mitomycin C, 79-5830
- Immunization**
 Anemia, Hemolytic
 Virus, Murine Leukemia, 79-5725
 Homologous Wasting Disease
 Virus, Murine Leukemia, 79-5725
 Lymphoma
 Virus, Marek's Disease Herpes
 79-5720
 Virus, Murine Leukemia
 Lymphocytes, 79-5725
 Virus, Papilloma
 Peptides, 79-5785
 Virus, SV40
 Concanavalin A, 79-5804
- Immunoglobulins**
 Gastritis
 Gastric Mucosa, 79-5841
 Metaplasia
 Gastric Mucosa, 79-5841
 Stomach Neoplasms
 Gastric Mucosa, 79-5841
- Immunologic Deficiency Syndromes**
 Leukemia
 Mutation, Mouse, 79-5823
 T-Lymphocytes
 Mutation, Mouse, 79-5823
- Immunosuppression**
 Gastrointestinal Neoplasms
 Plasmacytoma, 79-5908
 Neoplasms
 Kidney Failure, Chronic, 79-5944
 Nervous System Neoplasms
 Lymphoma, 79-5863
- Infectious Mononucleosis**
 Virus, Epstein-Barr
 DNA, Viral, 79-5780
- Insulin**
 Gastrointestinal Neoplasms
 Neoplastic Endocrine-Like Syndromes
 79-5483
- Interferon**
 Homologous Wasting Disease
 Virus, Polyoma, 79-5787
 Virus, Polyoma
 Anti-Antibodies, 79-5787
 Immune Response, Mouse, 79-5787
Xenopus laevis
 Oocytes, 79-5976
 RNA, Messenger, 79-5976
- Intestinal Neoplasms**
 Adenocarcinoma
 Methanol, (Methyl-*ONN*-azoxy)-,
 Acetate (Ester), 79-5516
 Morpholine, *N*-Nitroso-, 79-5593
 Adenoma
 Cell Transformation, Neoplastic
 79-5902
 Genetics, 79-5902
 Methanol, (Methyl-*ONN*-azoxy)-,
 Acetate (Ester), 79-5516
 Morpholine, *N*-Nitroso-, 79-5593
 Polyps, 79-5906
 Anatomic Distribution
 Epidemiology, 79-5946
 Carcinoid Tumor
 Case Report, 79-5903, 79-5905
 Carcinoma
 Polyps, 79-5906
 Leiomyosarcoma
 Case Report, 79-5904
 Neoplasm Metastasis, 79-5904
 Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
 Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-5516
 Polyps
 Histological Study, 79-5906
- Intestinal Polyps**
 Adenoma

Intestinal Polyps (cont'd)
 Cell Transformation, Neoplastic
 79-5902
Brain Neoplasms
 Glioblastoma Multiforme, 79-5873
Rectal Neoplasms
 Precancerous Conditions, 79-5958

Intestines, Small
 Carcinoma 256, Walker
 Growth, 79-5691
 Neoplasm Transplantation, 79-5691

Invertase
 see Sucrase

Iridium
 Radioisotopes
 Half-Life, 79-5683
 Lung Clearance, 79-5683

Iron
 Lung Neoplasms
 Adenocarcinoma, 79-5892
 Epidemiology, France, 79-5973
 Occupational Hazard, 79-5973

Islet Cell Tumor
 Virus, Polyoma, BK
 Carcinogenic Potential, Hamster
 79-5791

Isoenzymes
 Leukemia, Myeloblastic
 Glucose Dehydrogenases, 79-5859

Jaundice
 Toxins
 Food Contamination, 79-5960

Karyotyping
 Fibrosarcoma
 Virus, Herpes Simplex 2, 79-5775
 Virus, Polyoma, BK
 Cell Transformation, Neoplastic
 79-5790

Kelthane
 see Ethanol, 1,1-Bis(*p*-chlorophenyl)-
 2,2,2-trichloro-

Keratosis
 Mouth Neoplasms
 Retinol Palmitate, 79-5535

Kerosene
 Lymphocytes
 Mutagenic Activity, 79-5650
 Thioguanine Resistance, 79-5650

Kidney
 Hepatoma
 Abnormalities, 79-5916

Kidney Failure, Chronic
 Kidney Neoplasms
 Epidemiology, Review, 79-5500
 Neoplasms
 Epidemiology, 79-5944
 Hemodialysis, 79-5944
 Immunosuppression, 79-5944

Kidney Neoplasms
 Adenocarcinoma
 Erythropoietin, 79-5914
 1-Propanol, 2,3-Dibromo-, Phosphate
 79-5531
 Adenoma
 1-Propanol, 2,3-Dibromo-, Phosphate
 79-5531
 Carcinoma, Transitional Cell
p-Acetophenetidine, 79-5612
 Erythropoietin
 Neoplasm Metastasis, 79-5914
 Geographic Factors
 Epidemiology, 79-5945
 Ethnic Groups, 79-5945
 Kidney Failure, Chronic
 Epidemiology, Review, 79-5500
 Kidney, Polycystic
 Epidemiology, Review, 79-5500
 1-Propanol, 2,3-Dibromo-, Phosphate

Kidney Neoplasms (cont'd)
 Precancerous Conditions, 79-5531
 Socioeconomic Factors
 Epidemiology, 79-5945

Kidney, Polycystic
 Kidney Neoplasms
 Epidemiology, Review, 79-5500

Klippel-Trenaunay Disease
 Nephroblastoma
 Case Report, 79-5913

L Cells
 Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 DNA Replication, 79-5585
 Hybrid Cells
 Immunogenicity, Tumorigenicity
 79-5831
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 DNA Replication, 79-5585

Lactation
 Breast Neoplasms
 Epidemiology, Review, 79-5508
 Cholanthren-2-ol, 3-Methyl-
 Carcinogenic Metabolite, 79-5642
 Cholanthren, 1,2-Dihydroxy-3-methyl-
 Carcinogenic Metabolite, 79-5642

Lactic Acid
 Tubercidin
 Erythrocytes, 79-5977
 Virus, Avian Myeloblastosis
 Glycoproteins, 79-5706

Laryngeal Neoplasms
 Carcinoma, Epidermoid
 Epidemiology, 79-5888
 Genetics, 79-5888
 Ethyl Alcohol
 Epidemiology, 79-5888

IgA
 Serum Levels, 79-5844

Lymphocytes
 Acetylglucosaminidase, 79-5844
 Precancerous Conditions, 79-5844

Neutrophils
 Alkaline Phosphatase, 79-5844
 Glucuronidase, 79-5844
 Precancerous Conditions, 79-5844

Papilloma
 Immune Response, 79-5844

Smoking
 Epidemiology, 79-5888
 Ethyl Alcohol, 79-5889
 Neoplasm Metastasis, 79-5889
 Precancerous Conditions, 79-5889

Lead
 Occupational Hazard
 Teratogenic, Mutagenic Effect, Review
 79-5499
 Radioisotopes
 Epidemiology, Review, 79-5453
 Occupational Hazard, 79-5453

Leiomyoma
 Stomach Neoplasms
 Polyps, 79-5896

Leiomyosarcoma
 Duodenal Neoplasms
 Case Report, 79-5901
 Intestinal Neoplasms
 Case Report, 79-5904
 Neoplasm Metastasis, 79-5904

Leukemia
 Child
 Epidemiology, Review, 79-5493
 Hypercalcemia
 Bone Resorption, Review, 79-5511
 Immunity, Cellular
 Killer Cells, Review, 79-5460
 Immunologic Deficiency Syndromes
 Mutation, Mouse, 79-5823
 Radiation, Ionizing
 Antigens, Viral, 79-5754

Leukemia (cont'd)
 Reverse Transcriptase
 Precancerous Conditions, 79-5765
 Virus, Radiation Leukemia
 Antigens, Viral, 79-5754
 Virus, Rauscher Murine Leukemia
 Antigens, Viral, 79-5754

Leukemia, Lymphoblastic
 Age Factors
 Epidemiology, India, 79-5931
 Drug Therapy
 Chromosome Aberrations, 79-5513
 T-Lymphocytes
 Immune Response, 79-5828
 Surface Properties, 79-5828
 Pituitary Gland
 Neoplasm Circulating Cells, 79-5858
 Radiation, Ionizing
 Chromosome Aberrations, 79-5513

Leukemia, Lymphocytic
 Age Factors
 Epidemiology, India, 79-5931
 Amyloidosis
 Immune Response, Review, 79-5481
 Lymphosarcoma
 Cyclophosphamide, 79-5930
 Radiotherapy, 79-5930
p-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, HCl, 79-5930
 Vinblastine, 79-5930
 Vincristine, 79-5930

Leukemia, Monocytic
 Hodgkin's Disease
 Drug Therapy, Combination, 79-5866
 Radiation, Ionizing, 79-5866

Leukemia, Myeloblastic
 Age Factors
 Epidemiology, India, 79-5931
 Drug Therapy
 Chromosome Aberrations, 79-5513
 Glucose Dehydrogenases
 Granulocytes, 79-5859
 Isoenzymes, 79-5859
 Monocytes, 79-5859
 Hematopoietic Stem Cells
 Cell Differentiation, 79-5859
 Pituitary Gland
 Neoplasm Circulating Cells, 79-5858

Leukemia, Myelocytic
 Age Factors
 Epidemiology, India, 79-5931
 Antigens
 Blast Crisis, 79-5827
 Antigens, Neoplasm
 Cell Differentiation, 79-5824
 Benzene
 Carcinogenic Potential, Review
 79-5418
 Chromosomes, Human, 21-22
 Blast Crisis, 79-5827
 DNA, Neoplasm
 DNA-RNA Hybridization, 79-5982
 Nucleotide Sequence, 79-5982
 Drug Therapy
 Chromosome Aberrations, 79-5513
 Enzymes
 Erythrocytes, 79-5855
 Glucocorticoids
 Immune Response, Mouse, 79-5824
 Lipopolysaccharides
 Immune Response, Mouse, 79-5824
 B-Lymphocytes
 IgM, 79-5827
 Pyruvate Kinase
 Hematologic Diseases, 79-5855
 Metabolism, Inborn Errors, 79-5855
 Reverse Transcriptase
 Shay Tumor, 79-5982
 Sarcoma, Reticulum Cell
 Eosinophils, 79-5856
 Skin Neoplasms
 Case Report, 79-5857
 Toluene

Leukemia, Myelocytic (cont'd)
 Carcinogenic Potential, Review
 79-5418

Leukocytes
 Transplantation, Heterologous
 Cell Transformation, Neoplastic
 79-5826
 Fetal Blood, 79-5826
 Virus, Herpes Simplex
 Migration Inhibitory Factor, 79-5769

Leukoplakia
 Eye Neoplasms
 Classification, Review, 79-5477

Leukoplakia, Oral
 Neutrophils
 Immune Response, 79-5844

Lipoma
 Stomach Neoplasms
 Polyps, 79-5896

Lipopolysaccharides
 Corticosterone
 Lymphocytes, 79-5670
 Estradiol
 Lymphocytes, 79-5670
 Leukemia, Myelocytic
 Immune Response, Mouse, 79-5824
 Macrophages
 Activation, Review, 79-5461
 4,4'-Stilbenediol, α,α' -Diethyl-
 Lymphocytes, 79-5670

Lipoproteins
 Teratoid Tumor
 Receptors, LDL, 79-5988

Liver Cirrhosis
 Hepatoma
 Alpha Fetoproteins, 79-5959
 Australia Antigen, 79-5959
 Precancerous Conditions, Review
 79-5491
 Liver Neoplasms
 Epidemiology, 79-5943

Liver Diseases
 Bile Duct Neoplasms
 Precancerous Conditions, 79-5912
 Drugs
 Epidemiology, Review, 79-5436

Liver Neoplasms
 Adenoma
 Contraceptives, oral, 79-5441, 79-5443
 Alpha Fetoproteins
 Diagnosis and Prognosis, Review
 79-5465
 Angioma
 Hydrazine, 4-Hydroxymethylphenyl-
 79-5549
 Carcinogen, Chemical
 Occupational Hazard, Review, 79-5426
 Carcinogen, Environmental
 Kupffer Cells, Review, 79-5482
 Carcinoma
 Cyclohexane, 1,2,3,4,5,6-Hexachloro-,
 γ -Isomer, 79-5417
 Carcinoma, Ductal
 Precancerous Conditions, Review
 79-5491
 Ceruloplasmin
 Oxidoreductases, 79-5998
 Chinese
 Epidemiology, 79-5943
 Contraceptives, Oral
 Epidemiology, Review, 79-5442
 79-5443, 79-5503
 Precancerous Conditions, 79-5941
 Precancerous Conditions, Review
 79-5440
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 Dose-Response Study, Mouse, 79-5519
 Diethylamine, *N*-Nitroso-
 Animal Model, Fish, 79-5560
 Histological Study, 79-5560
 Drugs

Liver Neoplasms (cont'd)
 Precancerous Conditions, Review
 79-5436
 Estradiol, 17-Ethynyl-
 Diagnosis, Review, 79-5503
 Ethanol, 2-(2,4,5-Trichlorophenoxy)-
 Dose-Response Study, Mouse, 79-5519
 Ethyl Alcohol
 Epidemiology, Review, 79-5502
 Ethylene, Chloro-
 Adenosine Triphosphatase, 79-5528
 Precancerous Conditions, 79-5528
 Ethylene, Trichloro-
 Precancerous Conditions, 79-5528
 Growth
 Ceruloplasmin, 79-5998
 Hepatitis
 Precancerous Conditions, Review
 79-5426
 Histiocytoma
 Hydrazine, Methyl-, 79-5549
 Hydrocarbons, Chlorinated
 Environmental Hazard, Review
 79-5408
 Hyperplasia
 Contraceptives, Oral, 79-5443
 Liver Cirrhosis
 Epidemiology, 79-5943
 Mestranol
 Diagnosis, Review, 79-5503
 Morpholine, *N*-Nitroso-
 Frog, Fish, 79-5593
 Mycotoxins
 Epidemiology, Review, 79-5408
 79-5428, 79-5502
 Nitrosamines
 Environmental Hazard, Review
 79-5408
 Nitrous Acid, Sodium Salt
 Morpholine, 79-5593
 Precancerous Conditions
 Cells, Cultured, Review, 79-5492
 Epidemiology, 79-5942
 Soft Tissue Neoplasms
 Dog, Review, 79-5434
 Virus, Hepatitis
 Epidemiology, 79-5943
 Epidemiology, Review, 79-5502

Liver Regeneration
 Diethylamine, *N*-Nitroso-
 Polyribosomes, 79-5562

Lung Neoplasms
 Adenocarcinoma
 Acetic Acid, Methylnitrosaminomethyl
 Ester, 79-5550
 Amylases, 79-5890
 Cholanthrene, 3-Methyl-, 79-5642
 Hydrazine, 4-Hydroxymethylphenyl-
 79-5549
 Immunity, Cellular, 79-5845
 Iron, 79-5892
 Neoplasm Metastasis, 79-5914
 Occupational Hazard, 79-5892
 Smoking, 79-5963
 Transplantation, Heterologous
 79-5914
 Adenoma
 Benz(a)anthracene, 7,12-Dimethyl-
 79-5553
 Cholanthrene, 3-Methyl-, 79-5642
 Hydrazine, 4-Hydroxymethylphenyl-
 79-5549
 Ultrastructural Study, 79-5891
 Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-
 nitroso-, 79-5571
 Urea, 1-(2-Chloroethyl)-3,3-dimethyl-
 1-nitroso-, 79-5571
 Urea, Ethyl Nitroso-, 79-5891
 Urea, 1,3,3-Tris(2-chloroethyl)-1-
 nitroso-, 79-5571
 Age Factors
 Epidemiology, 79-5964
 Aluminum
 Occupational Hazard, 79-5939
 Amylases

Lung Neoplasms (cont'd)
 Immunohistochemical Study, 79-5890
 Arsenic
 Epidemiology, Review, 79-5498
 Asbestos
 Epidemiology, Review, 79-5404
 Asbestosis
 Precancerous Conditions, Review
 79-5404
 Ascitic Tumor
 Neoplasm Metastasis, 79-5641
 Benz(a)anthracene, 3,4-Dihydro-3,4-
 dihydroxy-
 Carcinogenic Metabolite, 79-5634
 Benz(a)anthracene, 3,4-Dihydroxy-1,2-
 oxy-1,2,3,4-tetrahydro-
 Carcinogenic Metabolite, 79-5634
 Benz(a)anthracene, 7,12-Dimethyl-
 Piperonyl Butoxide, 79-5553
 Britain
 Epidemiology, Review, 79-5493
 Carcinoma
 Immunity, Cellular, 79-5845
 Smoking, 79-5963
 Carcinoma, Bronchiolar
 Smoking, 79-5963
 Carcinoma, Epidermoid
 Acetophenone, 2-Amino-, 79-5673
 Immunity, Cellular, 79-5845
 Smoking, 79-5963
 Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
 1-nitroso-, 79-5571
 Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-
 nitroso-, 79-5571
 Cholanthrene, 3-Methyl-
 Horizontal Transmission, Milk
 79-5642
 Cicatrix
 Rib Fracture, 79-5695
 Diet
 Epidemiology, Japan, 79-5965
 Epidemiology
 Kentucky, 79-5936
 Mathematical Model, 79-5962
 Netherlands, 79-5962
 Hamartoma
 Case Report, 79-5893
 Iron
 Epidemiology, France, 79-5973
 Occupational Hazard, 79-5973
 Occupational Hazard
 Blacks, Review, 79-5495
 Plant Agglutinins
 Reaction, Cutaneous, 79-5845
 Siderosis
 Case Report, 79-5892
 Smoking
 Blacks, Review, 79-5495
 Epidemiology, 79-5940
 Retinol, 79-5965
 Switzerland
 Epidemiology, Review, 79-5497
 Uranium
 Epidemiology, 79-5690
 Histological Study, 79-5690
 Urea, Ethyl Nitroso-
 Transplacental Carcinogenesis
 79-5891
 Water, Heavy
 Carcinogenic Activity, Rat, 79-5676

Lupus Erythematosus, Discoid
 BCG
 Vaccine Therapy, 79-5884
 Benzenecetic Acid, α -Methyl-4-(2-
 methylpropyl)-
 Drug Therapy, 79-5884
 Melanoma
 Antinuclear Factors, 79-5884

Lymph Nodes
 Breast Neoplasms
 Antigens, Neoplasm, 79-5849
 Carcinoma 256, Walker
 Lymphatic Metastasis, 79-5865
 Virus, Feline Sarcoma
 Antibodies, 79-5837

Lymph Nodes (cont'd)
Immunity, Cellular, 79-5837

Lymphatic Metastasis
Carcinoma 256, Walker
Lymph Nodes, 79-5865

Lymphocyte Depletion
Virus, Feline Leukemia
Prednisolone, Methyl-, 79-5759

Lymphocyte Transformation
Neoplasms
Plant Agglutinins, 79-5838
Virus, Avian Leukosis
Antigenic Determinants, 79-5825
Virus, Avian Myeloblastosis
Antigenic Determinants, 79-5825
Virus, Epstein-Barr
Antigens, Viral, 79-5784
DNA, Viral, 79-5779
Strain Difference, 79-5784
Virus, Murine Mammary Tumor
Glycoproteins, 79-5731
Virus, Rous Sarcoma
Antigenic Determinants, 79-5825

Lymphocytes
Adriamycin
Chromatids, 79-5573
Benzene
Chromatids, 79-5605
Benzo(a)pyren-3-ol
Metabolism, 79-5660
Benzo(a)pyrene
Mutagenic Activity, 79-5650
Benzo(a)pyrene-1,6-dione
Metabolism, 79-5660
Benzo(a)pyrene-3,6-dione
Metabolism, 79-5660
Bleomycin
Chromatids, 79-5540
1,4-Butanediol, Dimethylsulfonate
Chromatids, 79-5573
Butyric Acid, 4-(*p*-Bis(2-chloroethyl)aminophenyl)-
Chromatids, 79-5540
Chromosome Aberrations
Cell Cycle Kinetics, 79-5530
Corticosterone
Concanavalin A, 79-5670
Lipopolysaccharides, 79-5670
Cyclopenta(cd)pyrene
Mutagenic Activity, 79-5650
Cyclophosphamide
Chromatids, 79-5573
Cytosine, 1- β -D-Arabinofuranosyl-
Chromatids, 79-5540
Dimethylamine, *N*-Nitroso-
Chromosome Aberrations, 79-5575
Estradiol
Concanavalin A, 79-5670
Lipopolysaccharides, 79-5670
Ethylene, Chloro-
Chromosome Aberrations, 79-5575
Ethyleneimine
Chromosome Aberrations, 79-5530
Fotrin
Chromosome Aberrations, 79-5530
Hepatoma
Transplantation Immunology, 79-5704
Imidazole-1-ethanol, 2-Methyl-5-nitro-
Chromosome Aberrations, 79-5586
79-5587
Kerosene
Mutagenic Activity, 79-5650
Thioguanine Resistance, 79-5650
Laryngeal Neoplasms
Acetylglucosaminidase, 79-5844
Precancerous Conditions, 79-5844
Melanoma
Immunity, Cellular, 79-5991
Methotrexate
Chromatids, 79-5540
Mitomycin C
Chromatids, 79-5540, 79-5675
Chromosome Aberrations, 79-5675
Phosphamide

Lymphocytes (cont'd)
Chromosome Aberrations, 79-5530
Phosphine Oxide, 1,4-
Piperazinediylbis(bis(1-aziridinyl))-
Chromosome Aberrations, 79-5530
Phosphine Sulfide, Tris(1-aziridinyl)-
Chromatids, 79-5540
Chromosome Aberrations, 79-5530
Radiation, Ionizing
Chromatids, 79-5675
Chromosome Aberrations, 79-5675
Radon
Chromosome Aberrations, 79-5679
4,4'-Stilbenediol, α,α' -Diethyl-
Concanavalin A, 79-5670
Lipopolysaccharides, 79-5670
Toluene
Chromatids, 79-5605
Urea, Methyl Nitroso-
Chromosome Aberrations, 79-5575
Virus, Abelson Murine Leukemia
Reverse Transcriptase, 79-5737
Virus, Murine Leukemia
Immunization, 79-5725

B-Lymphocytes
Leukemia, Myelocytic
IgM, 79-5827
Lymphoma
Graft vs Host Reaction, 79-5826
Oncogenic Viruses
Paraproteins, Review, 79-5464
Virus, Avian Reticuloendotheliosis
Antigen-Antibody Reactions, 79-5719
Cell Transformation, Neoplastic
79-5719
Virus, Herpes Papio
DNA, Circular, 79-5768
Virus, Marek's Disease Herpes
Antilymphocyte Serum, 79-5723

T-Lymphocytes
Colonic Neoplasms
Antilymphocyte Serum, 79-5547
Cortisone
Immune Response, Review, 79-5462
Cortisone Acetate
Immunity, Passive, 79-5833
Fibrosarcoma
Antigens, Neoplasm, 79-5834
DNA Nucleotidyltransferases, 79-5833
Growth, 79-5833
Histocompatibility Antigens, 79-5834
Immunity, Passive, 79-5833
Immunologic Deficiency Syndromes
Mutation, Mouse, 79-5823
Leukemia, Lymphoblastic
Immune Response, 79-5828
Surface Properties, 79-5828
Lymphoma
Chicken, 79-5720
Graft vs Host Reaction, 79-5826
Killer Cells, Review, 79-5460
Plasmacytoma
Immunity, Passive, 79-5830
Thymus Gland
Transplantation, Review, 79-5462
Virus, AKR Murine Leukemia
Suppressor Cells, Review, 79-5455
Virus, Avian Leukosis
Immunity, Cellular, 79-5825
Virus, Avian Myeloblastosis
Immunity, Cellular, 79-5825
Virus, Feline Leukemia
Immunologic Capping, 79-5761
Virus, Friend Murine Leukemia
Suppressor Cells, Review, 79-5455
Virus, Gross Murine Leukemia
Transplantation Immunology, 79-5744
Virus, Marek's Disease Herpes
Antilymphocyte Serum, 79-5723
Virus Replication, 79-5724
Virus, Rous Sarcoma
Immunity, Cellular, 79-5825
Virus, SV40
Concanavalin A, 79-5804
Histocompatibility Antigens, 79-5803

T-Lymphocytes (cont'd)
Virus, Turkey Herpes
Virus Replication, 79-5724

Lymphoma (General and Unspecified)
see also Hodgkin's Disease
Aluminum
Occupational Hazard, 79-5939
Azathioprine
Case Report, 79-5863
Benz(a)anthracene, 7,12-Dimethyl-
Piperonyl Butoxide, 79-5553
Virus, Murine Leukemia, 79-5728
Brain Neoplasms
Virus, Epstein-Barr, 79-5783
Britain
Epidemiology, Review, 79-5493
Cholanthrene, 3-Methyl-
Antigen-Antibody Reactions, 79-5835
Hematopoietic Stem Cells
Immunity, Passive, 79-5460
Hypercalcemia
Bone Resorption, Review, 79-5511
B-Lymphocytes
Graft vs Host Reaction, 79-5826
T-Lymphocytes
Chicken, 79-5720
Graft vs Host Reaction, 79-5826
Killer Cells, Review, 79-5460
Macrophages
Lymphocyte Sensitization, 79-5829
Mycosis Fungoides
Case Report, 79-5864
Nervous System Neoplasms
Immunosuppression, 79-5863
Vasculitis, 79-5863
Paraproteins
Isolation and Characterization, Review
79-5464
Pituitary Gland
Neoplasm Circulating Cells, 79-5858
Radiation Ionizing
Lymphocyte Sensitization, 79-5829
Sarcoidosis
Case Report, 79-5861
Thymus Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-5728
Virus, AKR Murine Leukemia
Immunity, Cellular, Review, 79-5455
Virus, C-Type RNA Tumor
Virus, Helper, 79-5821
Virus, Epstein-Barr
Mouse, Nude, 79-5783
Transplantation, Heterologous
79-5783
Virus, Gibbon Ape Lymphoma
Antigenic Determinants, 79-5821
Virus, Marek's Disease Herpes
DNA-RNA Hybridization, 79-5722
DNA, Viral, 79-5722
Immunization, 79-5720
Virus, Murine Leukemia
Isolation and Characterization, Tissue
Culture, 79-5728
Neoplasm Regression, 79-5725
Virus, Radiation Leukemia
Macrophages, 79-5829
Replication Defective Mutants
79-5726
Virus, Helper, 79-5726
Virus, Rous-Associated
Carcinogenic Potential, 79-5720
Virus, Simian Sarcoma
Antigenic Determinants, 79-5821

Lymphomatoid Papulosis
Skin Neoplasms
Case Report, 79-5860

Lymphosarcoma
Autoimmune Diseases
Pure Red Cell Aplasia, 79-5862
Benzene
Occupational Hazard, 79-5932
Hematologic Diseases
Pure Red Cell Aplasia, 79-5862
Leukemia, Lymphocytic

Lymphosarcoma (cont'd)

- Cyclophosphamide, 79-5930
- Radiotherapy, 79-5930
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, HCl, 79-5930
- Vinblastine, 79-5930
- Vincristine, 79-5930
- Pure Red Cell Aplasia
- Case Report, 79-5862
- Virus, Herpes Simplex 2
- Isolation and Characterization, 79-5777
- Tree Shrew, 79-5777

Lysosomes

- Virus, Adeno 4
- HeLa Cells, 79-5812
- Virus Replication, 79-5812
- Virus, Adeno 31
- HeLa Cells, 79-5812
- Virus Replication, 79-5812
- Virus, SV40
- Acid Phosphatase, 79-5805
- Cytopathogenic Effect, Viral, 79-5805

Macrophages

- Asbestos
- Hydrolases, 79-5533
- Beryllium
- Hydrolases, 79-5533
- Complement
- Antitumor Activity, Review, 79-5461
- Endotoxins
- Activation, Review, 79-5461
- Histocompatibility Antigens
- Immune Response, Review, 79-5463
- Lipopolysaccharides
- Activation, Review, 79-5461
- Lymphokines
- Antitumor Activity, Review, 79-5461
- Lymphoma
- Lymphocyte Sensitization, 79-5829
- Virus, Radiation Leukemia, 79-5829
- Virus, Marek's Disease Herpes
- Uridine, 2'-Deoxy-5-iodo-, 79-5723
- Virus Replication, 79-5723

Maleic Acid, Diethyl Ester

- Styrene
- Ames Test, 79-5608

Mammary Neoplasms, Experimental

- Adenocarcinoma
- Epiglycanin, 79-5847
- Epiglycanin, Isolation and Characterization, 79-5848
- Adenofibroma
- Acetic Acid, Methylnitrosaminomethyl Ester, 79-5550
- Antineoplastic Agents
- Clone Cells, 79-5999
- Benz(a)anthracene, 7,12-Dimethyl-
- Collagen, 79-5636
- Propionitrile, 3-Amino-, 79-5636
- Receptors, Hormone, 79-5637
- Carcinoma, Papillary
- Estrone, 79-5997
- Progesterone, 79-5997
- Ceruloplasmin
- Oxidoreductases, 79-5998
- Endrin
- Carcinogenic Potential, Review, 79-5434
- Ergocryptine, 2-Bromo-
- Prolactin, 79-5997
- Estradiol
- Receptors, Hormone, 79-5637
- Estrus
- Strain Differences, Mouse, 79-5665
- Formamide, *N,N*-Dimethyl-
- Cell Differentiation, 79-5999
- Glycoproteins
- Growth, 79-5847
- Histocompatibility Antigens, 79-5848
- Neoplasm Transplantation, 79-5847
- 79-5848
- Growth
- Ceruloplasmin, 79-5998

Mammary Neoplasms, Experimental (cont'd)

- Hyperplasia
- Virus, Murine Mammary Tumor, 79-5732
- Prolactin
- Metabolism, 79-5663
- Transplantation, Homologous
- Fetal Mesenchyma, 79-5732
- Virus, Murine Leukemia
- Antigens, Viral, 79-5735
- Virus, Murine Mammary Tumor
- Antigen-Antibody Reactions, 79-5731
- Antigens, Viral, 79-5735
- Carbamic Acid, Ethyl Ester, 79-5734
- DNA-RNA Hybridization, 79-5733
- Horizontal Transmission, 79-5736
- Immunity, Cellular, 79-5731
- Parity, 79-5736
- Prolactin, 79-5734
- Radiation, Ionizing, 79-5734

Manganese

- Plasmacytoma
- DNA Polymerase, 79-5986

Mannans

- see Polysaccharides

Melanocytes

- Aging
- Cell Division, 79-5992
- Diphenol Oxidases, 79-5992
- Cell Division
- Choroid, Monkey, 79-5992
- Melanoma
- Ultrastructural Study, 79-5992
- Nevus, Pigmented
- Ultrastructural Study, 79-5992

Melanoma

- Contraceptives, Oral
- Neoplasm Metastasis, 79-5672
- DOPA Oxidase
- Transplantation, Heterologous, 79-5879
- Ultrastructural Study, 79-5879
- Eye Neoplasms
- Case Report, 79-5875
- Classification, Review, 79-5477
- Glaucoma, 79-5875
- Melanosis, 79-5877
- Genetics
- Case Report, 79-5881
- Hybrid Cells
- Antigens, 79-5839
- Chromosomes, 79-5839
- Tumorigenicity, 79-5839
- Lupus Erythematosus, Discoid
- Antinuclear Factors, 79-5884
- Lymphocytes
- Immunity, Cellular, 79-5991
- Melanocytes
- Ultrastructural Study, 79-5992
- Melittin
- Pigmentation, 79-5624
- Nevus, Pigmented
- Case Report, 79-5882
- Cell Transformation, Neoplastic, 79-5878
- Histological Study, 79-5880
- Precancerous Conditions, Review, 79-5480
- Pituitary Gland
- Neoplasm Metastasis, 79-5871
- Pregnancy
- Neoplasm Metastasis, 79-5672
- Transplantation, Heterologous
- Chromosome Abnormalities, 79-5991
- Growth, 79-5991
- Mouse, Nude, 79-5991
- Ultraviolet Rays
- Age Factors, Review, 79-5446
- Virus, Polio
- Cytopathogenic Effect, Viral, 79-5991

Melanosis

- Eye Neoplasms

Melanosis (cont'd)

- Case Report, 79-5877
- Melanoma, 79-5877

Melatonin

- Pinealoma
- Radioimmunoassay, 79-5664

Melittin

- 5,8,11,14-Eicosatetraenoic Acid
- Metabolism, Fibroblasts, 79-5624
- Melanoma
- Pigmentation, 79-5624
- Prostaglandins E
- Metabolism, Fibroblasts, 79-5624

Membrane Proteins

- Adenocarcinoma
- Fucose, 79-6000
- Colonic Neoplasms
- Glucosamine, 79-6000

Meningeal Neoplasms

- Carcinoma
- Case Report, 79-5874

Meningioma

- Chromosome Aberrations
- Chromosomes, Human, 21-22, 79-5806
- Virus, SV40
- Antigens, Neoplasm, 79-5806

Mercapturic Acid

- see Cysteine, *N*-Acetyl-

Mercury

- Environmental Hazard
- Epidemiology, Review, 79-5433

Mesenchymoma

- Morpholine, *N*-Nitroso-
- Frog, Fish, 79-5593

Mesothelioma

- Asbestos
- Epidemiology, Review, 79-5404
- Pleural Neoplasms
- Asbestos, 79-5974
- Asbestosis, 79-5975
- Epidemiology, Turkey, 79-5974

Mestranol

- Hepatoma
- Contraceptives, Oral, 79-5941
- Liver Neoplasms
- Diagnosis, Review, 79-5503

Metaplasia

- Cell Differentiation
- Gene Regulation, Review, 79-5473
- Gastric Mucosa
- Immunoglobulins, 79-5841
- Prostate
- Cholanthere, 3-Methyl-, 79-5644
- Retinoic Acid, 79-5644
- Stomach Neoplasms
- Epidemiology, Japan, 79-5504
- Guanidine, 1-Propyl-3-nitro-1-nitroso-79-5591

Methane, Dichloro-

- Chick Embryo
- Teratogenic Effect, 79-5523

Methane, Sulfinylbis-

- Neuroblastoma
- Glycoproteins, 79-5984

Methanesulfonic Acid, Methyl Ester

- Agrobacterium tumefaciens*
- Transformation, Genetic, 79-5576
- 1,4-Butanediol, Dimethylsulfonate
- Alkaline Elution Assay, 79-5577
- Endonucleases
- DNA Repair, 79-5628
- Granuloma
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, 79-5577
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
- DNA Repair, 79-5586
- Mitomycin C
- Alkaline Elution Assay, 79-5577

Methanesulfonic Acid, Methyl Ester
(cont'd)

- Virus, Simian Adeno 7
DNA, Viral, 79-5640
- Virus, SV40
DNA, Viral, 79-5797

Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)

- Intestinal Neoplasms
Adenocarcinoma, 79-5516
Adenoma, 79-5516
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-5516
- Microsomes, Liver
Proteins, 79-5517
- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Alcohol Oxidoreductases, 79-5516
- Polyribosomes
Proteins, 79-5517
RNA, Messenger, 79-5517

Methanol, (Methyl-*ONN*-azoxy)-

- Ames Test
Glucuronic Acid Conjugate, 79-5515

Methemoglobinemia

- Nitric Acid
Food Contamination, 79-5926

Methotrexate

- Chromatids
Lymphocytes, 79-5540
- Guanidine, 1-Propyl-3-nitro-1-nitroso-
Guanyl Cyclase, 79-5590
- Hydrazine
Guanyl Cyclase, 79-5590
- Radiotherapy
Chromosome Aberrations, 79-5512

Methyl(acetoxymethyl)nitrosamine

- see Acetic Acid, Methylnitrosaminomethyl Ester

2-(4'-Methyl)benzoylaminofluorene

- see Phthalamic Acid, 2-(4'-Methyl)-

Metronidazole

- see Imidazole-1-ethanol, 2-Methyl-5-nitro-

Microsomes

- Barbituric Acid, 5-Ethyl-5-phenyl-
Aryl Hydrocarbon Hydroxylases
79-5532
NADPH Cytochrome C Reductase
79-5532
- UDP Glucuronosyltransferase, 79-5532
- Benz(a)anthracene
Aryl Hydrocarbon Hydroxylases
79-5657
- Benz(a)anthracene, 7,12-Dimethyl-
Aryl Hydrocarbon Hydroxylases
79-5657
- Benzo(a)pyrene
Metabolism, Fibroblasts, 79-5657
- Cholanthrene, 3-Methyl-
Aryl Hydrocarbon Hydroxylases
79-5532
NADPH Cytochrome C Reductase
79-5532
- UDP Glucuronosyltransferase, 79-5532
- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Epoxide Hydratases, 79-5604

Microsomes, Liver

- Acetamide, *N*-Fluorenyl-3-yl-
Metabolism, 79-5556
- Acetamide, *N*-(9-Hydroxyfluorenyl-3-yl)-
Metabolism, 79-5556
- Acetamide, *N*-(9-Oxofluorenyl-3-yl)-
NADH, NADPH Oxidoreductases
79-5556
- Aflatoxin B1
Carcinogenic Metabolite, 79-5618
- Barbituric Acid, 5-Ethyl-5-phenyl-
Cytochrome P-450, 79-5638
- Benz(a)anthracene, 7,12-Dimethyl-
Phenol Metabolites, 79-5631
- Benzene, (Epoxyethyl)-

Microsomes, Liver (cont'd)

- Ames Test, 79-5608
- Barbituric Acid, 5-Ethyl-5-phenyl-
79-5602
- Benzo(a)pyren-3-ol
Cholanthrene, 3-Methyl-, 79-5653
- Benzo(a)pyren-9-ol
Cholanthrene, 3-Methyl-, 79-5653
- 1,1'-Biphenyl, 2,2',5,5'-Tetrachloro-
Proteins, Binding, 79-5616
- Cholanthrene, 3-Methyl-
Aryl Hydrocarbon Hydroxylases
79-5609
Cytochrome P-450, 79-5638
Epoxide Hydratases, 79-5609
- p*-Cresol, 2,6-Di-*tert*-butyl-
Aryl Hydrocarbon Hydroxylases
79-5600
Cytochrome Reductases, 79-5600
Oxidoreductases, 79-5600
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Aryl Hydrocarbon Hydroxylases
79-5519
- Dimethylamine, *N*-Nitroso-
Proteins, 79-5517
- Ethanol, 2-(2,4,5-Trichlorophenoxy)-
Aryl Hydrocarbon Hydroxylases
79-5519
- Ethyl Alcohol
Aryl Hydrocarbon Hydroxylases
79-5518
Cytochrome P-450, 79-5518
NADPH Cytochrome C Reductase
79-5518
- Ethylene, 1,1-Bis(*p*-chlorophenyl)-
Mutagenic Metabolite, 79-5526
- Ethylene, Chloro-
RNA, Binding, 79-5528
- Ethylene, Trichloro-
RNA, Binding, 79-5528
- Furan, 2-(*N*-Ethylcarbamoyloxymethyl)-
Carcinogenic Metabolite, 79-5618
- Methanol, (Methyl-*ONN*-azoxy)-, Ace-
tate (Ester)
Proteins, 79-5517
- Smoking
Aryl Hydrocarbon Hydroxylases
79-5518
- Styrene
Aryl Hydrocarbon Hydroxylases
79-5609
Epoxide Hydratases, 79-5609

Milk Proteins

- Xenopus laevis*
Oocytes, 79-5976
RNA, Messenger, 79-5976

Mineral Oil

- see Petroleum

Mitochondria

- Carcinogen, Chemical
Saccharomyces cerevisiae, 79-5514
- Virus, Rous Sarcoma
Virus Replication, 79-5714

Mitogens

- 4,4'-Stilbenediol, α,α' -Diethyl-
Immune Response, Mouse, 79-5670

Mitomycin C

- Chromatids
Cell Cycle Kinetics, 79-5540
- Lymphocytes, 79-5540
- Down's Syndrome
Chromosome Aberrations, 79-5675
- Lymphocytes
Chromatids, 79-5675
Chromosome Aberrations, 79-5675
- Methanesulfonic Acid, Methyl Ester
Alkaline Elution Assay, 79-5577
- Plasmacytoma
Immunity, Passive, 79-5830

Mitosis

- Adelphane
Chromosome Aberrations, 79-5611
- Ultraviolet Rays

Mitosis (cont'd)

- Chromosome Aberrations, 79-5680

Monocytes

- Benzo(a)pyren-9-ol
Metabolism, 79-5660
- Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
Metabolism, 79-5660
- Leukemia, Myeloblastic
Glucose Dehydrogenases, 79-5859

Morpholine

- Liver Neoplasms
Nitrous Acid, Sodium Salt, 79-5593

Morpholine, *N*-Nitroso-

- Hepatoma
Frog, Fish, 79-5593
- Precancerous Conditions, 79-5489
- Intestinal Neoplasms
Adenocarcinoma, 79-5593
Adenoma, 79-5593
- Liver Neoplasms
Frog, Fish, 79-5593
- Mesenchymoma
Frog, Fish, 79-5593

Mouth Neoplasms

- Benz(a)anthracene, 7,12-Dimethyl-
Radiation, Ionizing, 79-5685
- Carcinoma, Epidermoid
Benz(a)anthracene, 7,12-Dimethyl-
79-5630
- Hyperplasia
Retinol Palmitate, 79-5535
- Keratosis
Retinol Palmitate, 79-5535
- Retinol Palmitate
Calcium Oxide, 79-5535
Tobacco, 79-5535
- Transplantation, Homologous
Antilymphocyte Serum, 79-5630
- Neoplasm Invasiveness, 79-5630

Multiple Myeloma

- Hypercalcemia
Bone Resorption, Review, 79-5511

Mutagens

- p*-Cresol, 2,6-Di-*tert*-butyl-
Ames Test, 79-5599
Enzyme Activation, 79-5599
- DNA
Bioassays, Review, 79-5424
- Ellipticine
Ames Test, 79-5646
- Ellipticine, 9-Fluoro-
Ames Test, 79-5646
- Environmental Hazard
Risk Evaluation, Review, 79-5429
- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Ames Test, 79-5599
Enzyme Activation, 79-5599
- Smoking
Urine, 79-5580

Mutation

- Benzene, (Epoxyethyl)-
Methyl-, Chloro- Derivatives, 79-5598
- Thioguanine Resistance, 79-5598
- Carcinogen, Chemical
Threshold Limit Values, Review
79-5445
- Nitrous Acid, Sodium Salt
Escherichia coli, 79-5557
Salmonella typhimurium, 79-5557
- Platinum, Diamminedichloro-, *cis*-
Hamster V79 Cells, 79-5542
- Radiation, Ionizing
Threshold Limit Values, Review
79-5445
- Ultraviolet Rays
Fibroblasts, Review, 79-5448
- Virus, Adeno 2
DNA, Viral, 79-5809
- Virus, Adeno 5
DNA, Viral, 79-5809

Mycosis Fungoides

- Genetics
- Epidemiology, 79-5933
- Lymphoma
- Case Report, 79-5864
- Occupational Hazard
- Epidemiology, 79-5933
- Ultraviolet Rays
- Hypersensitivity, 79-5933

Mycotoxins

- Food Contamination
- Epidemiology, Review, 79-5428
- Liver Neoplasms
- Epidemiology, Review, 79-5408
- 79-5428, 79-5502

Myelofibrosis

- Benzene
- Carcinogenic Potential, Review
- 79-5418
- Reverse Transcriptase
- Isolation and Characterization
- 79-5765
- Toluene
- Carcinogenic Potential, Review
- 79-5418

Myeloproliferative Disorders

- Radium
- Dose-Response Study, Dog, 79-5678
- Strontium
- Dose-Response Study, Dog, 79-5678

NADPH Cytochrome C Reductase

- Barbituric Acid, 5-Ethyl-5-phenyl-
- Microsomes, 79-5532
- Cholanthrene, 3-Methyl-
- Microsomes, 79-5532
- Ethyl Alcohol
- Microsomes, Liver, 79-5518

Nafoxidine

- Receptors, Hormone
- Carcinogenic, Teratogenic Potential,
- Review, 79-5438

2-Naphthylamine

- Ames Test
- Mutagenic Activity, 79-5617
- DNA Repair
- Mutagenic Activity, 79-5617
- Food Additives
- Carcinogenic Potential, Review
- 79-5403

Nasopharyngeal Neoplasms

- Virus, Epstein-Barr
- DNA, Viral, 79-5780

Necrosis

- Aflatoxin B1
- Parenchymal Cells, Liver, 79-5619
- Carcinoma
- Blood Circulation, 79-5994
- Neoplasm Transplantation, 79-5994

Neocarcinostatin

- Ames Test
- Urinary Metabolite, 79-5574

Neoplasm Circulating Cells

- Hodgkin's Disease
- Pituitary Gland, 79-5858
- Leukemia, Lymphoblastic
- Pituitary Gland, 79-5858
- Leukemia, Myeloblastic
- Pituitary Gland, 79-5858
- Lymphoma
- Pituitary Gland, 79-5858

Neoplasm Metastasis

- Bone Neoplasms
- Site Distribution, Review, 79-5479
- Brain Neoplasms
- Blacks, 79-5937
- Carcinoma, Bronchogenic, 79-5937
- Choriocarcinoma, 79-5937
- Breast Neoplasms
- Pituitary Gland, 79-5871

Neoplasm Metastasis (cont'd)

- Choriocarcinoma
- Case Report, 79-5920
- Eye Neoplasms
- Choriocarcinoma, 79-5920
- Head and Neck Neoplasms
- Diagnosis, Review, 79-5478
- Hepatoma
- Morris Tumor, Review, 79-5407
- Hypersensitivity, Delayed, 79-5838
- Intestinal Neoplasms
- Leiomyosarcoma, 79-5904
- Kidney Neoplasms
- Erythropoietin, 79-5914
- Laryngeal Neoplasms
- Smoking, 79-5889
- Lung Neoplasms
- Adenocarcinoma, 79-5914
- Ascitic Tumor, 79-5641
- Melanoma
- Contraceptives, Oral, 79-5672
- Pituitary Gland, 79-5871
- Pregnancy, 79-5672
- Neuroblastoma
- Clone Cells, Review, 79-5475
- Mouse, Review, 79-5475
- Pituitary Gland, 79-5871
- Ovarian Neoplasms
- Choriocarcinoma, 79-5920
- Teratoid Tumor, 79-5919
- Prostatic Neoplasms
- Blacks, 79-5937
- Sarcoma
- Lymph Nodes, Review, 79-5479
- Teratoid Tumor
- Peritoneum, 79-5919

Neoplasm Recurrence, Local

- Eye Neoplasms
- Surgery, Operative, 79-5875
- Sarcoma
- Wounds and Injuries, 79-5885

Neoplasm Transplantation

- BCG
- Necrosis, Review, 79-5459
- Carcinoma
- Growth, 79-5994
- Necrosis, 79-5994
- Carcinoma, Epidermoid
- Cholanthrene, 3-Methyl-, 79-5641
- Carcinoma 256, Walker
- Intestines, Small, 79-5691
- Colonic Neoplasms
- Hydrazine, 1,2-Dimethyl-, 79-5843
- Hepatoma
- Virus, Avian Leukosis, 79-5701
- Mammary Neoplasms, Experimental
- Glycoproteins, 79-5847, 79-5848
- Sarcoma
- Cholanthrene, 3-Methyl-, 79-5641

Neoplasms (General and Unspecified)

- Anemia, Pernicious
- Epidemiology, 79-5853
- Case-Control Study
- Epidemiology, Review, 79-5498
- Diet
- Epidemiology, Review, 79-5496
- Endocrinology
- Mouse, Nude, Review, 79-5472
- Growth
- Mouse, Nude, Review, 79-5469
- Kidney Failure, Chronic
- Epidemiology, 79-5944
- Hemodialysis, 79-5944
- Immunosuppression, 79-5944
- Plant Agglutinins
- Lymphocyte Transformation, 79-5838
- Smoking
- Epidemiology, Review, 79-5496
- Transplantation, Heterologous
- Mouse, Nude, Review, 79-5469
- 79-5472
- Tuberculin
- Hypersensitivity, Delayed, 79-5838
- Virus, Adeno 7
- DNA-DNA Hybridization, 79-5817

Neoplasms (General and Unspecified) (cont'd)

- Virus, Adeno 11
- DNA-DNA Hybridization, 79-5817

Neoplasms, Experimental

- BCG
- Immunity, Cellular, 79-5459
- Carcinogen, Chemical
- Dose-Response Study, Review
- 79-5419
- Human Risk Factors, Review, 79-5425
- Mouse, Nude, Review, 79-5471
- Immune Response
- Oncogenic Viruses, 79-5471
- Microvasculature
- Immunity, Cellular, 79-5459
- Radiation
- Dose-Response Study, Review
- 79-5419
- Virus, Adeno 7
- DNA, Viral, 79-5817
- Virus, Friend Spleen Focus-Forming
- Virus, Moloney Murine Sarcoma
- 79-5471
- Virus, Moloney Murine Sarcoma
- Mouse, Nude, Review, 79-5471
- Virus, Polyoma
- Mouse, Nude, Review, 79-5471

Neoplasms, Multiple Primary

- Age Factors
- Epidemiology, 79-5964
- Bladder Neoplasms
- Smoking, 79-5970
- Colonic Neoplasms
- Hydrazine, 1,2-Dimethyl-, 79-5547
- Hodgkin's Disease
- Case Report, 79-5866
- Parotid Neoplasms
- Carcinoma, 79-5872

Neoplasms, Radiation-Induced

- Nuclear Reactors
- Risk Factors, Review, 79-5452
- Occupational Hazard
- Statistical Analysis, 79-5934
- Plutonium
- Epidemiology, Review, 79-5450
- Radiation, Ionizing
- Dose-Response Study, 79-5689
- Radioactive Fallout
- Epidemiology, Review, 79-5450
- Radiotherapy
- Epidemiology, Review, 79-5450
- Sarcoma, Osteogenic
- Virus, C-Type RNA Tumor, 79-5693

Neoplasms, Multiple Primary

- Gynecologic Neoplasms
- Case Report, 79-5917

Neoplastic Endocrine-Like Syndromes

- Amyloidosis
- Diagnosis, Review, 79-5481
- Gastrointestinal Neoplasms
- Glucagon, 79-5483
- Insulin, 79-5483
- Peptides, Review, 79-5483
- Somatotropin Release Inhibiting Hormone, 79-5483
- Parathyroid Neoplasms
- Adenoma, 79-5868
- Thyroid Neoplasms
- Carcinoma, 79-5868
- Hypercalcemia, 79-5868

Nephroblastoma

- Child
- Epidemiology, Review, 79-5493
- Kidney Transplantation
- Case Report, 79-5846
- Klippel-Trenaunay Disease
- Case Report, 79-5913

Nerve Tissue Proteins

- Brain Neoplasms
- Cells, Cultured, 79-5983
- Neuroglia

- Nerve Tissue Proteins (cont'd)**
Cell Transformation, Neoplastic
79-5983
- Nervous System Neoplasms**
Lymphoma
Immunosuppression, 79-5863
Vasculitis, 79-5863
Neurilemmoma
Acetic Acid, Methylnitrosaminomethyl
Ester, 79-5550
Teratogenic Effect
Dose-Response Study, Rat, 79-5570
Urea, Ethyl Nitroso-
Transplacental Carcinogenesis
79-5570
Vasculitis
Adrenal Cortex Hormones, 79-5863
- Neurilemmoma**
Acetic Acid, Methylnitrosaminomethyl
Ester
Administration Route, Rat, 79-5550
Duodenal Ulcer
Precancerous Conditions, 79-5900
Nervous System Neoplasms
Acetic Acid, Methylnitrosaminomethyl
Ester, 79-5550
Pyloric Stenosis
Precancerous Conditions, 79-5900
Stomach Neoplasms
Case Report, 79-5900
Urea, Ethyl Nitroso-
Ultrastructural Study, 79-5925
- Neuroblastoma**
Cell Differentiation
Glycoproteins, 79-5984
Cells, Cultured
Acetylcholinesterase, 79-5984
Choline Acetyltransferase, 79-5984
Methane, Sulfinylbis-
Glycoproteins, 79-5984
Neoplasm Metastasis
Clone Cells, Review, 79-5475
Mouse, Review, 79-5475
Pituitary Gland
Neoplasm Metastasis, 79-5871
- Neurofibromatosis**
Nevus, Pigmented
Precancerous Conditions, Review
79-5480
Pituitary Neoplasms
Adenoma, Eosinophilic, 79-5869
- Neuroglia**
Cell Transformation, Neoplastic
Cells, Cultured, 79-5983
Nerve Tissue Proteins, 79-5983
- Neutrophils**
Laryngeal Neoplasms
Alkaline Phosphatase, 79-5844
Glucuronidase, 79-5844
Precancerous Conditions, 79-5844
- Nevus, Pigmented**
Carcinoma, Basal Cell
Precancerous Conditions, Review
79-5480
Melanocytes
Ultrastructural Study, 79-5992
Melanoma
Case Report, 79-5882
Cell Transformation, Neoplastic
79-5878
Histological Study, 79-5880
Precancerous Conditions, Review
79-5480
Neurofibromatosis
Precancerous Conditions, Review
79-5480
- Nickel Sulfide**
Chromosome Aberrations
Chromium Trioxide, 79-5536
- Nicotine, 1'-Demethyl-1'-nitroso-**
Ames Test
- Nicotine, 1'-Demethyl-1'-nitroso- (cont'd)**
Hydroxy Derivatives, Review, 79-5414
Esophageal Neoplasms
Tobacco Alkaloids, Review, 79-5414
Respiratory Tract Neoplasms
Tobacco Alkaloids, Review, 79-5414
- Nitric Acid**
Food Contamination
Fertilizers, 79-5926
Methemoglobinemia
Food Contamination, 79-5926
- Nitrogen**
Urea, Ethyl Nitroso-
Hydrogen Bonding, 79-5568
- Nitrogen Dioxide**
Antipyrine, 4-(Dimethylamino)-
Nitrosation, 79-5546
- Nitrogen Mustard Oxide**
see Diethylamine, 2,2'-Dichloro-*N*-
methyl-, *N*-Oxide
- Nitromin**
see Diethylamine, 2,2'-Dichloro-*N*-
methyl-, *N*-Oxide
- Nitrosamines**
Environmental Hazard
Carcinogenic Potential, Review
79-5410, 79-5413
Food Contamination
Quantitation Method, Review, 79-5411
Liver Neoplasms
Environmental Hazard, Review
79-5408
Nitrous Acid
Food Contamination, Review, 79-5410
Photolysis
Radicals, Review, 79-5409
Structure-Activity Relationship
Carcinogenic Potential, Review
79-5412
- Nitroso Compounds**
Photolysis
Radicals, Review, 79-5409
- Nitrous Acid**
Nitrosamines
Food Contamination, Review, 79-5410
- Nitrous Acid, Sodium Salt**
Liver Neoplasms
Morpholine, 79-5593
Mutation
Escherichia coli, 79-5557
Salmonella typhimurium, 79-5557
Phenol
DNA, Mutagenic Activity, 79-5557
Polyamines
DNA, Mutagenic Activity, 79-5557
- Norharman**
Benzo(a)pyrene
Metabolism, Lung, 79-5655
5*H*-Pyrido(4,3*b*)indole, 3-Amino-1-
methyl-
DNA, binding, 79-5582
- Nose Neoplasms**
Carcinoma, Epidermoid
Cesium Radioisotopes, 79-5684
Strontium, 79-5684
Yttrium Radioisotopes, 79-5684
- Nuclear Reactors**
Neoplasms, Radiation-Induced
Risk Factors, Review, 79-5452
Plutonium
Risk Factors, Review, 79-5452
- Nucleic Acids**
Acetamide, *N*-(Acetyloxy)-*N*-(4-(2-
phenylethenyl)phenyl)-
Alkylation Reactions, 79-5555
Nucleoside Adducts, 79-5555
Carcinogen, Chemical
Mutagenic Activity, Review, 79-5422
- Nucleic Acids (cont'd)**
Fibrosarcoma
Virus, Herpes Simplex 2, 79-5775
- Nucleoproteins**
Gynecologic Neoplasms
DNA, 79-5996
- Nucleoside Deaminases**
Guanosine, *O*-Methyl-2'-deoxy-
Cytosol, Rat, 79-5588
Demethylation, 79-5588
- Nucleoside-5-triphosphatase**
see Adenosine Triphosphatase
- Nucleotides, Cyclic**
Breast Diseases
Theophylline, 79-5596
Papilloma
Alanine, 3-(3,4-Dihydroxyphenyl)-
79-5632
BCG, 79-5632
Dibutyl Cyclic AMP, 79-5632
Skin Neoplasms
Papilloma, 79-5632
- Occupational Hazard**
Acetic Acid, (2,4-Dichlorophenoxy)-
Herbicides, Review, 79-5413
Adenocarcinoma
Wood, 79-5971
Asbestosis
Epidemiology, 79-5975
Benzene
Chromosome Aberrations, 79-5605
Epidemiology, 79-5932
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-5910
Brain Neoplasms
Aluminum, 79-5939
Cadmium
Toxicity, 79-5935
Carcinogen, Chemical
Risk Evaluation, Review, 79-5510
Teratogenic Effect, Review, 79-5437
Dimethylamine, *N*-Nitroso-
Herbicides, Review, 79-5413
Dipropylamine, *N*-Nitroso-
Herbicides, Review, 79-5413
Ethanol, *N*-Nitrosoiminodi-
Carcinogenic Potential, Review
79-5413
Ethylene, Trichloro-
Epidemiology, Review, 79-5401
Hodgkin's Disease
Benzene, 79-5932
Lead
Radioisotopes, 79-5453
Teratogenic, Mutagenic Effect, Review
79-5499
Lung Neoplasms
Adenocarcinoma, 79-5892
Aluminum, 79-5939
Blacks, Review, 79-5495
Iron, 79-5973
Lymphoma
Aluminum, 79-5939
Lymphosarcoma
Benzene, 79-5932
Mycosis Fungoides
Epidemiology, 79-5933
Neoplasms, Radiation-Induced
Statistical Analysis, 79-5934
Pancreatic Neoplasms
Aluminum, 79-5939
Paranasal Sinus Neoplasms
Epidemiology, Sweden, 79-5601
Wood, 79-5601
Polonium
Epidemiology, Review, 79-5453
Radiation, Ionizing
Epidemiology, 79-5934
Radioisotopes
Chromosome Aberrations, 79-5605
Radon
Epidemiology, Review, 79-5453
Sarcoma, Reticulum Cell

Occupational Hazard (cont'd)

- Benzene, 79-5932
- Toluene
 - Chromosome Aberrations, 79-5605
 - Metabolism, Review, 79-5418

Oligodendroglioma

- Brain Neoplasms
 - Urea, Methyl Nitroso-, 79-5566

Oncogenic Viruses

- Cell Transformation, Neoplastic
- Mouse, Nude, Review, 79-5470
- Genetics
 - Risk Factors, Review, 79-5474
- B-Lymphocytes
 - Paraproteins, Review, 79-5464
- Neoplasms, Experimental
- Immune Response, 79-5471
- Urogenital Neoplasms
 - Co-carcinogenic Effect, Review 79-5420

Ornithine

- Glioma
 - Peptide Synthesis, 79-5980

Ornithine Decarboxylase

- Diethylamine, *N*-Nitroso-
Liver, Rat, 79-5563

Osteoclastoma

- see* Giant Cell Tumors

Osteomyelitis

- Bone Neoplasms
 - Carcinoma, 79-5887
 - Case Report, 79-5887

Ovarian Neoplasms

- Blood Groups
 - Genetics, 79-5955
- Carcinoma
 - Cyclohexane, 1,2,3,4,5,6-Hexachloro-,
γ-Isomer, 79-5417
- Choriocarcinoma
 - Neoplasm Metastasis, 79-5920
- Cystadenoma
 - Ploidies, 79-5918
 - Ultrastructural Study, 79-5918
- Diabetes Mellitus
 - Epidemiology, 79-5955
- Genetics
 - Epidemiology, 79-5955
- Granulosa Cell Tumor
 - Acetophenone, 2-Amino-, 79-5673
- Parity
 - Epidemiology, 79-5955
- Polyps
 - Precancerous Conditions, 79-5955
- Teratoid Tumor
 - Neoplasm Metastasis, 79-5919
 - Ultrastructural Study, 79-5919
- Virus, Mumps
 - Immune Response, 79-5954

Oxidoreductases

- Barbituric Acid, 5-Ethyl-5-phenyl-
Liver, Rat Fetus, 79-5638
- Cholanthrene, 3-Methyl-
Liver, Rat Fetus, 79-5638
- p*-Cresol, 2,6-Di-*tert*-butyl-
Microsomes, Liver, 79-5600
- Liver Neoplasms
 - Ceruloplasmin, 79-5998
- Mammary Neoplasms, Experimental
- Ceruloplasmin, 79-5998

Oxygen

- Urea, Ethyl Nitroso-
Hydrogen Bonding, 79-5568

Pancreatic Neoplasms

- Aluminum
 - Occupational Hazard, 79-5939
- Anorexia
 - Diagnosis, Review, 79-5468
- Carcinoma, Ductal
 - Epidemiology, Review, 79-5501
- Ultrasonics

Pancreatic Neoplasms (cont'd)

- Diagnosis, Review, 79-5501

Pancreatitis

- Alcoholic Beverages
- Epidemiology, 79-5972
- Diet
 - Epidemiology, 79-5972

Papilloma

- Alanine, 3-(3,4-Dihydroxyphenyl)-
Nucleotides, Cyclic, 79-5632
- BCG*
 - Nucleotides, Cyclic, 79-5632
- Brain Neoplasms
 - Virus, Polyoma, BK, 79-5791
- Cervix Neoplasms
 - Case Report, 79-5923
- Dibutyl Cyclic AMP
 - Nucleotides, Cyclic, 79-5632
- Esophageal Neoplasms
 - Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
1-nitroso-, 79-5571
 - Urea, 1-(2-Chloroethyl)-3,3-dimethyl-
1-nitroso-, 79-5571
- Skin Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-
79-5632, 79-5633
 - Nucleotides, Cyclic, 79-5632
- Stomach Neoplasms
 - Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
1-nitroso-, 79-5571
 - Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-
nitroso-, 79-5571
 - Urea, 1-(2-Chloroethyl)-3,3-dimethyl-
1-nitroso-, 79-5571
 - Urea, 1,3,3-Tris(2-chloroethyl)-1-
nitroso-, 79-5571
- Tongue Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-
79-5685
 - Radiation, Ionizing, 79-5685

Paranasal Sinus Neoplasms

- Occupational Hazard
- Epidemiology, Sweden, 79-5601
- Wood
 - Occupational Hazard, 79-5601

Paraproteinemia

- Pyoderma Gangrenosum
- IgG, 79-5840

Paraproteins

- Amino Acids
 - Isolation and Characterization, Review 79-5464
- Autoimmune Diseases
 - Isolation and Characterization, Review 79-5464
- Hodgkin's Disease
 - Isolation and Characterization, Review 79-5464
- Lymphoma
 - Isolation and Characterization, Review 79-5464

Parathyroid Hormone

- Bone Neoplasms
 - Hypercalcemia, 79-5511

Parathyroid Neoplasms

- Adenoma
 - Neoplastic Endocrine-Like Syndromes 79-5868

Parity

- Mammary Neoplasms, Experimental
- Virus, Murine Mammary Tumor 79-5736
- Ovarian Neoplasms
 - Epidemiology, 79-5955

Parotid Neoplasms

- Carcinoma
 - Neoplasms, Multiple Primary, 79-5872

Peptic Ulcer

- Stomach Neoplasms
 - Precancerous Conditions, Review

Peptic Ulcer (cont'd)

- Precancerous Conditions, Review 79-5484

Peptide Hydrolases

- Androgens
 - Receptors, Hormone, 79-5979

Peptides

- Fibrosarcoma
 - Virus, Herpes Simplex 2, 79-5775
- Teratoid Tumor
 - Collagen, 79-5990
- Virus, Herpes Simplex 1
 - DNA Polymerase, 79-5771
- Virus, Kirsten Murine Sarcoma
 - Binding Sites, 79-5748
- Cell Transformation, Neoplastic 79-5748
- Temperature Sensitive Mutants 79-5748
- Virus, Murine Mammary Tumor
- Viral Proteins, 79-5730
- Virus, Papilloma
 - Immunization, 79-5785
- Warts
 - Virus, Papilloma, 79-5785

Peroxidases

- Teratoid Tumor
 - Rosette Formation, 79-5989

Pesticides

- Carcinogenic Potential
 - Risk Evaluation, Review, 79-5432
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-
chlorophenyl)-
Carcinogenic Potential, Review 79-5402

Petroleum

- Adenocarcinoma
 - Transplantation, Heterologous 79-5832
- Plasmacytoma
 - Transplantation, Heterologous 79-5832
- Transplantation Immunology, 79-5832

Phagocytosis

- Carcinogen, Environmental
- Kupffer Cells, Review, 79-5482

Pharyngeal Neoplasms

- Carcinoma, Epidermoid
- Diverticulosis, 79-5895

Phenelzine

- see* Hydrazine, Phenethyl-

Phenol

- Nitrous Acid, Sodium Salt
- DNA, Mutagenic Activity, 79-5557

Phenol, (1,1-Dimethylethyl)-4-methoxy-

- Benzene, 1,2-Dichloro-4-nitro-
Glutathione Transferases, 79-5604
- Benzene, (Epoxethyl)-
Epoxide Hydratases, 79-5604

- Microsomes, 79-5604

- Glutathione Transferases

- Cytosol, 79-5604

- Intestinal Neoplasms

- Methanol, (Methyl-*ONN*-azoxy)-,
Acetate (Ester), 79-5516

- Methanol, (Methyl-*ONN*-azoxy)-, Ace-
tate (Ester)

- Alcohol Oxidoreductases, 79-5516

- Mutagens

- Ames Test, 79-5599

- Enzyme Activation, 79-5599

- Radiation, Ionizing

- Chromosome Aberrations, 79-5603

- Sulphydryl Compounds

- Intestinal Mucosa, 79-5604

Phenol, 4-Methoxy-

- Radiation, Ionizing
- Chromosome Aberrations, 79-5603

Phenol, *p*-Nitro-
Acetamide, *N*-Fluoren-2-yl-
Metabolism, Liver, 79-5551

Phosphamide
Chromosome Aberrations
Lymphocytes, 79-5530

Phosphine Oxide, 1,4-
Piperazinediylbis(bis(1-aziridinyl))-
Chromosome Aberrations
Lymphocytes, 79-5530

Phosphine Sulfide, Tris(1-aziridinyl)-
Ames Test
Urinary Metabolite, 79-5574
Bladder Neoplasms
DNA Replication, 79-5539
Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-, 79-5539
Chromatids
Chromosome Aberrations, 79-5575
Lymphocytes, 79-5540
Chromosome Aberrations
Lymphocytes, 79-5530

Phosphoproteins
Virus, Avian Sarcoma
Cell Transformation, Neoplastic
79-5707
Protein Kinase, 79-5707
Virus, Harvey Murine Sarcoma
Antigenic Determinants, 79-5749
Virus, Kirsten Murine Sarcoma
Antigenic Determinants, 79-5749
Temperature Sensitive Mutants
79-5749
Virus, Murine Sarcoma
Protein Kinase, 79-5729
Virus, Rat Sarcoma
Antigenic Determinants, 79-5749
Virus, SV40
Antigens, Neoplasm, 79-5801

Phosphoric Acid, 2-Chloro-1-(2,4,5-trichlorophenyl)vinyl Dimethyl
Angiosarcoma
Histological Study, Mouse, 79-5538
Hepatosarcoma
Histological Study, Mouse, 79-5538

Phosphorofluoridic Acid, Bis(1-methylethyl) Ester
Androgens
Receptors, Hormone, 79-5979
Prostatic Neoplasms
Receptors, Hormone, 79-5979

Phosphorus Radioisotopes
Eye Neoplasms
Diagnosis, 79-5985

Phthalamic Acid, *N*-Fluoren-2-yl-
Hepatosarcoma
Growth, Review, 79-5407

Phthalamic Acid, 2-(4'-Methyl)-
Hepatosarcoma
Growth, Review, 79-5407

Pinealoma
Melatonin
Radioimmunoassay, 79-5664

Piperonyl Butoxide
Acetohydroxamic Acid, *N*-4-Biphenyl-
Hepatocarcinogenicity, 79-5553
Acetohydroxamic Acid, *N*-Fluoren-2-yl-
Hepatocarcinogenicity, 79-5553
Hepatosarcoma
Acetamide, *N*-Fluoren-2-yl-, 79-5553
Acetanilide, 4'-Phenyl-, 79-5553
Lung Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-5553
Lymphoma
Benz(a)anthracene, 7,12-Dimethyl-
79-5553

Pituitary Gland
Breast Neoplasms

Pituitary Gland (cont'd)
Neoplasm Metastasis, 79-5871
Hodgkin's Disease
Neoplasm Circulating Cells, 79-5858
Leukemia, Lymphoblastic
Neoplasm Circulating Cells, 79-5858
Leukemia, Myeloblastic
Neoplasm Circulating Cells, 79-5858
Lymphoma
Neoplasm Circulating Cells, 79-5858
Melanoma
Neoplasm Metastasis, 79-5871
Neuroblastoma
Neoplasm Metastasis, 79-5871

Pituitary Hormones, Review
Uterine Neoplasms
Diabetes Mellitus, 79-5485

Pituitary Neoplasms
Adenoma
Prolactin, 79-5595
Somatotropin, 79-5595
Adenoma, Eosinophilic
Neurofibromatosis, 79-5869
Adenomatosis, Familial Endocrine
Case Report, 79-5870
Carcinoma
Cyclohexane, 1,2,3,4,5,6-Hexachloro-,
 γ -Isomer, 79-5417
Contraceptives, Oral
Amenorrhea, Review, 79-5494
Endrin
Carcinogenic Potential, Review
79-5434

Placenta
Benzo(a)pyrene, 7,8-Dihydro-9,10-oxy-
7,8,9,10-tetrahydro-
DNA Adduct, 79-5661

Plant Agglutinins
Lung Neoplasms
Reaction, Cutaneous, 79-5845
Neoplasms
Lymphocyte Transformation, 79-5838
Tuberculosis, Pulmonary
Reaction, Cutaneous, 79-5845

Plant Tumors
Agrobacterium tumefaciens
DNA-RNA Hybridization, 79-5981
Extrachromosomal Inheritance
79-5981

Plasmacytoma
DNA Polymerase
Manganese, 79-5986
Thymine Nucleotides, 79-5986
Fibrosarcoma
Hybrid Cells, 79-5831
Gastrointestinal Neoplasms
Immunosuppression, 79-5908
Transplantation, 79-5908
Histocompatibility Antigens
Immunogenicity, 79-5830
Hybrid Cells
Immunogenicity, Tumorigenicity
79-5831
IgA
Virus-Like Particles, 79-5820
Immunity, Passive
Hybrid Cells, 79-5830
T-Lymphocytes, 79-5830
Mitomycin C, 79-5830
Petroleum
Transplantation, Heterologous
79-5832
Transplantation Immunology, 79-5832
Virus, C-Type RNA Tumor
DNA-RNA Hybridization, 79-5820
Virus-Like Particles, 79-5820

Plasminogen Activators
Cell Transformation, Neoplastic
Mouse, Nude, Review, 79-5469

Platinum, Diamminedichloro-, *cis*-
Ames Test

Platinum, Diamminedichloro-, *cis*-(cont'd)
Mutagenic Activity, 79-5541
DNA
Alkaline Elution Assay, 79-5542
Mutation
Hamster V79 Cells, 79-5542

Pleural Neoplasms
Mesothelioma
Asbestos, 79-5974
Asbestosis, 79-5975
Epidemiology, Turkey, 79-5974

Plutonium
Chelating Agents
Body Burden, 79-5682
Fluoride
Inhalation Study, Dog, 79-5682
Neoplasms, Radiation-Induced
Epidemiology, Review, 79-5450
Nuclear Reactors
Risk Factors, Review, 79-5452
Tissue Distribution
Lactation, 79-5686
Maternal-Fetal Exchange, 79-5686

Polonium
Body Burden
Mathematical Model, 79-5697
Occupational Hazard
Epidemiology, Review, 79-5453

Polyamines
Nitrous Acid, Sodium Salt
DNA, Mutagenic Activity, 79-5557

Polychlorobiphenyl Compounds
Aryl Hydrocarbon Hydroxylases
Spodoptera eridania, 79-5648
Spectrum Analysis
Hydroxyl Derivatives, 79-5614

Polycythemia
Adenocarcinoma
Erythropoietin, 79-5914
Transplantation, Heterologous
79-5914

Polynucleotides
Acetamide, *N*-(Acetyloxy)-*N*-(4-(2-phenylethenyl)phenyl)-
Alkylation Reactions, 79-5555
Urea, Ethyl Nitroso-
Alkylation, 79-5568

Polyps
Cervix Neoplasms
Precancerous Conditions, 79-5922
Intestinal Neoplasms
Adenoma, 79-5906
Carcinoma, 79-5906
Histological Study, 79-5906
Ovarian Neoplasms
Precancerous Conditions, 79-5955
Rectal Neoplasms
Carcinoma, 79-5909
Carcinoma In Situ, 79-5909
Precancerous Conditions, 79-5909
Stomach Neoplasms
Granuloma, 79-5896
Leiomyoma, 79-5896
Lipoma, 79-5896

Polyribosomes
Diethylamine, *N*-Nitroso-
Liver Regeneration, 79-5562
RNA, Messenger, 79-5562
Methanol, (Methyl-*ONN*-azoxy)-, Ace-
tate (Ester)
Proteins, 79-5517
RNA, Messenger, 79-5517

Polysaccharides
Teratoid Tumor
Rosette Formation, 79-5989

Precancerous Conditions
Aflatoxin B1
DNA Replication, 79-5619
Bile Duct Neoplasms

Precancerous Conditions (cont'd)

- Colitis, 79-5912
- Liver Diseases, 79-5912
- Breast Neoplasms**
 - Immunity, Cellular, 79-5849
- Cervix Neoplasms**
 - Condylomata Acuminata, 79-5921
 - Epidemiology, 79-5922
 - Immunity, Cellular, 79-5850
 - Polyps, 79-5922
 - Sex Behavior, Review, 79-5509
- Condylomata Acuminata**
 - Virus, Papilloma, 79-5921
- Gynecologic Neoplasms**
 - Cytodiagnosis, 79-5953
- Hepatoma**
 - Acetamide, *N*-Fluorenyl-2-yl-, 79-5489
 - Contraceptives, Oral, 79-5942
 - Diethylamine, *N*-Nitroso-, 79-5489
 - DNA Replication, 79-5561
 - Morpholine, *N*-Nitroso-, 79-5489
 - Ultrastructural Study, Review, 79-5489
- Kidney Neoplasms**
 - 1-Propanol, 2,3-Dibromo-, Phosphate 79-5531
- Laryngeal Neoplasms**
 - Lymphocytes, 79-5844
 - Neutrophils, 79-5844
 - Smoking, 79-5889
- Leukemia**
 - Reverse Transcriptase, 79-5765
- Liver Neoplasms**
 - Cells, Cultured, Review, 79-5492
 - Contraceptives, Oral, 79-5941
 - Epidemiology, 79-5942
 - Ethylene, Chloro-, 79-5528
 - Ethylene, Trichloro-, 79-5528
- Neurilemmoma**
 - Duodenal Ulcer, 79-5900
 - Pyloric Stenosis, 79-5900
- Ovarian Neoplasms**
 - Polyps, 79-5955
- Rectal Neoplasms**
 - Intestinal Polyps, 79-5958
 - Polyps, 79-5909
- Stomach Neoplasms**
 - Carcinoma, 79-5504
 - Gastrectomy, 79-5488
- Vaginal Neoplasms**
 - Estradiol, 3-Benzoyl-, 79-5669
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 79-5668, 79-5669
- Prednisolone, Methyl-**
 - Virus, Feline Leukemia
 - Antigen-Antibody Reactions, 79-5759
 - Lymphocyte Depletion, 79-5759
- Pregnancy**
 - Breast Neoplasms**
 - Epidemiology, Review, 79-5508
 - Estradiol, 79-5508
 - Progesterone, 79-5508
 - Melanoma**
 - Neoplasm Metastasis, 79-5672
- Procollagen**
 - Extrachromosomal Inheritance
 - RNA, Messenger, 79-5716
 - Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic 79-5716
 - RNA, Messenger, 79-5712, 79-5716
- Progestational Hormones**
 - Gynecologic Neoplasms
 - Carcinogenic Potential, Review 79-5442
 - Uterine Neoplasms
 - Epidemiology, Review, 79-5439
- Progesterone**
 - Breast Neoplasms**
 - Pregnancy, 79-5508
 - Mammary Neoplasms, Experimental
 - Carcinoma, Papillary, 79-5997
- Prolactin**
 - Adenoma

Prolactin (cont'd)

- Theophylline, 79-5595
- Thyrotropin Releasing Hormone 79-5595
- Immune Serums
- Radioimmunoassay, 79-5663
- Mammary Neoplasms, Experimental
- Ergocryptine, 2-Bromo-, 79-5997
- Metabolism, 79-5663
- Virus, Murine Mammary Tumor 79-5734
- Pituitary Neoplasms
- Adenoma, 79-5595
- Propane, 1,2-Epoxy-3,3,3-trichloro-**
 - Styrene
 - Ames Test, 79-5608
- 1-Propanol, 2,3-Dibromo-, Phosphate**
 - Kidney Neoplasms
 - Adenocarcinoma, 79-5531
 - Adenoma, 79-5531
 - Precancerous Conditions, 79-5531
- Propionitrile, 3-Amino-**
 - Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 79-5636
- Prostaglandins**
 - Bone Neoplasms
 - Hypercalcemia, 79-5511
- Prostaglandins E**
 - Melittin
 - Metabolism, Fibroblasts, 79-5624
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - Adenosine Cyclic 3',5' Monophosphate, 79-5625
 - Metabolism, Fibroblasts, 79-5624
- Prostate**
 - Metaplasia
 - Cholanthrene, 3-Methyl-, 79-5644
 - Retinoic Acid, 79-5644
- Prostatic Hypertrophy**
 - Cholanthrene, 3-Methyl-
 - Retinoic Acid, 79-5644
- Prostatic Neoplasms**
 - Androgens
 - Receptors, Hormone, 79-5979
 - Neoplasm Metastasis
 - Blacks, 79-5937
 - Phosphorofluoric Acid, Bis(1-methylethyl) Ester
 - Receptors, Hormone, 79-5979
- Protein Kinase**
 - Diethylamine, *N*-Nitroso-
 - Adenosine Cyclic 3',5' Monophosphate, 79-5563
 - Virus, Avian Sarcoma
 - Phosphoproteins, 79-5707
 - Virus, Moloney Murine Sarcoma
 - Reverse Transcriptase, 79-5751
 - Virus, Murine Sarcoma
 - Actin, 79-5729
 - Phosphoproteins, 79-5729
 - Tubulin, 79-5729
 - Virus, SV40
 - Antigens, Neoplasm, 79-5801
- Proteins**
 - Dimethylamine, *N*-Nitroso-
 - Microsomes, Liver, 79-5517
 - Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
 - Microsomes, Liver, 79-5517
 - Polyribosomes, 79-5517
- Psoralen, 8-Methoxy-**
 - Skin Neoplasms
 - Photochemotherapy, Review, 79-5447
- Psoralen, 4,5',8-Trimethyl-**
 - Ultraviolet Rays
 - Chromatids, 79-5692
 - DNA Adducts, 79-5692

Purine, 2-Amino-6-methoxy-

- DNA Repair
- Enzyme Induction, 79-5579
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
- DNA Repair, 79-5579
- Escherichia coli*, 79-5589
- Triazene, 1-Methyl-3-phenyl-
- Brain, Rat, 79-5584
- Urea, Methyl Nitroso-
- DNA Repair, 79-5567, 79-5579
- Purine-6-thiol**
 - Ames Test
 - Microsomes, Liver, 79-5574
- Pyloric Stenosis**
 - Neurilemmoma
 - Precancerous Conditions, 79-5900
 - Stomach Neoplasms
 - Case Report, 79-5900
- Pyoderma Gangrenosum**
 - Paraproteinemia
 - IgG, 79-5840
- Pyrazole**
 - Pyrrolidine, 1-Nitroso-
 - Metabolism, 79-5578
- 3,6-Pyridazinedione, 1,2-Dihydro-**
 - Chromosome Aberrations
 - Hamster V79 Cells, 79-5610
 - Potassium, Diethanolamine Salts 79-5610
- Pyridine, 4-(*p*-Nitrobenzyl)-**
 - Ethylene Oxide, 1,1-Bis(*p*-chlorophenyl)-
 - Alkylating Activity, 79-5526
- 5*H*-Pyrido(4,3*b*)indole, 3-Amino-1-methyl-**
 - Harman
 - DNA, binding, 79-5582
 - Norharman
 - DNA, binding, 79-5582
- Pyrimidine Nucleotides**
 - Xeroderma Pigmentosum
 - Fibroblasts, 79-5993
- Pyrene, 2-Oxo-3-hydroxy-**
 - Structure-Activity Relationship
 - Carcinogenic Activity, 79-5594
- Pyrrolidine, 1-Nitroso-**
 - Ames Test
 - Hydroxy Derivatives, Review, 79-5414
 - Carbamic Acid, Diethyldithio-
 - Metabolism, 79-5578
 - Ethyl Alcohol
 - Metabolism, 79-5578
 - Food Contamination
 - Carcinogenic Potential, Review 79-5412
- Pyrazole**
 - Metabolism, 79-5578
 - Respiratory Tract Neoplasms
 - Tobacco Alkaloids, Review, 79-5414
 - Tissue Distribution
 - Autoradiography, Mouse, 79-5578
- Pyruvate Kinase**
 - Leukemia, Myelocytic
 - Hematologic Diseases, 79-5855
 - Metabolism, Inborn Errors, 79-5855
- Quinoline, 4-Nitro-, 1-Oxide**
 - Carcinoma, Ehrlich Tumor
 - Sulphydryl Compounds, 79-5592
 - Glutathione
 - Toxicity, 79-5592
 - Sulphydryl Compounds
 - Metabolism, 79-5592
- Radiation**
 - Mathematical Model
 - Dose-Response Study, Review 79-5419
 - Neoplasms, Experimental
 - Dose-Response Study, Review 79-5419

Radiation, Ionizing

- Abnormalities
 - Mutagenic Activity, 79-5689
- Anemia, Aplastic
 - Chromosome Aberrations, 79-5851
- Ataxia Telangiectasia
 - Chromosome Aberrations, 79-5851
 - Chromosomes, Review, 79-5444
- Bone Neoplasms
 - Carcinoma, 79-5449
 - Epidemiology, Review, 79-5449
 - Fibrosarcoma, 79-5449
 - Sarcoma, 79-5449
- 2,3-Butanediol, 1,4-Dimercapto-DNA Repair, 79-5688
- Caffeine
 - DNA Photolyase, 79-5688
 - Escherichia coli*, 79-5688
- Chondrosarcoma
 - Epidemiology, Review, 79-5449
- Down's Syndrome
 - Chromosome Aberrations, 79-5675
 - 79-5851
- Dwarfism
 - Chromosome Aberrations, 79-5851
- Gallic Acid, Propyl Ester
 - Chromosome Aberrations, 79-5603
- Genetics
 - Dose-Response Study, 79-5689
 - Risk Factors, Review, 79-5474
- Hepatoma
 - Case Report, Fetus, 79-5696
- Leukemia
 - Antigens, Viral, 79-5754
 - Leukemia, Lymphoblastic
 - Chromosome Aberrations, 79-5513
 - Leukemia, Monocytic
 - Hodgkin's Disease, 79-5866
 - Lymphocytes
 - Chromatids, 79-5675
 - Chromosome Aberrations, 79-5675
 - 79-5851
 - Lymphoma
 - Lymphocyte Sensitization, 79-5829
 - Mammary Neoplasms, Experimental
 - Virus, Murine Mammary Tumor
 - 79-5734
 - Mouth Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-79-5685
 - Mutation
 - Threshold Limit Values, Review
 - 79-5445
 - Neoplasms, Radiation-Induced
 - Dose-Response Study, 79-5689
 - Occupational Hazard
 - Epidemiology, 79-5934
 - Phenol, (1,1-Dimethylethyl)-4-methoxy-Chromosome Aberrations, 79-5603
 - Phenol, 4-Methoxy-Chromosome Aberrations, 79-5603
- Retinoblastoma
 - Chromosomes, Review, 79-5444
- Sarcoma, Osteogenic
 - Epidemiology, Review, 79-5449
- Spermatozoa
 - Morphology, Review, 79-5421
- Thymine
 - Mutagenic Derivative, 79-5581
- Tongue Neoplasms
 - Co-carcinogenic Effect, 79-5685
- Papilloma, 79-5685
- Urogenital Neoplasms
 - DNA Repair, Review, 79-5420
- Virus, Reo 3
 - RNA Polymerase, 79-5687
 - Virus Activation, 79-5687

Radioactive Fallout

- Cesium Radioisotopes
 - Greenland, 79-5927
- Chromosome Aberrations
 - G-Banding, 79-5681
- Food Contamination
 - Greenland, 79-5927
- Neoplasms, Radiation-Induced
 - Epidemiology, Review, 79-5450

Radioactive Fallout (cont'd)

- Strontium
 - Greenland, 79-5927

Radioisotopes

- Benzene
 - Chromosome Aberrations, 79-5605
- Iridium
 - Half-Life, 79-5683
 - Lung Clearance, 79-5683
- Lead
 - Epidemiology, Review, 79-5453
 - Occupational Hazard, 79-5453
- Occupational Hazard
 - Chromosome Aberrations, 79-5605

Radiotherapy

- Leukemia, Lymphocytic
 - Lymphosarcoma, 79-5930
- Methotrexate
 - Chromosome Aberrations, 79-5512
- Trophoblastic Tumor
 - Chromosome Aberrations, 79-5512
- Ultrasonics
 - Carcinogenic Potential, Review
 - 79-5451

Radium

- Myeloproliferative Disorders
 - Dose-Response Study, Dog, 79-5678
- Sarcoma, Osteogenic
 - Dose-Response Study, Dog, 79-5678
 - Virus-Like Particles, 79-5693

Radon

- Chromosome Aberrations
 - Lymphocytes, 79-5679
 - Water Supply, 79-5679
- Occupational Hazard
 - Epidemiology, Review, 79-5453

Receptors, Hormone

- Androgens
 - Peptide Hydrolases, 79-5979
 - Phosphorofluoridic Acid, Bis(1-methylethyl) Ester, 79-5979
 - Prostate, Testis, Rat, 79-5979
- Breast Neoplasms
 - Estradiol, 79-5637
- Carcinogenic, Teratogenic Potential, Review
 - Estrogen Agonists, Review, 79-5438
- Estradiol
 - Estrogen Agonists, Review, 79-5438
 - 4,4'-Stilbenediol, α,α' -Diethyl-79-5637
- Estril
 - Estrogen Agonists, Review, 79-5438
- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-79-5637
 - Estradiol, 79-5637
- Nafoxidine
 - Carcinogenic, Teratogenic Potential, Review, 79-5438
- Prostatic Neoplasms
 - Androgens, 79-5979
 - Phosphorofluoridic Acid, Bis(1-methylethyl) Ester, 79-5979
 - 4,4'-Stilbenediol, α,α' -Diethyl-79-5637
 - Estrogen Agonists, Review, 79-5438

Rectal Neoplasms

- Adenocarcinoma
 - Genetics, 79-5899
- Carcinoma
 - Epidemiology, 79-5958
 - Polyps, 79-5909
- Carcinoma In Situ
 - Polyps, 79-5909
- Genetics
 - Case Report, 79-5899
- Intestinal Polyps
 - Precancerous Conditions, 79-5958
- Polyps
 - Precancerous Conditions, 79-5909

Reserpine

- Breast Neoplasms

Reserpine (cont'd)

- Epidemiology, Review, 79-5435

Respiratory Tract Neoplasms

- 1-Butanone, 4-(Methylnitrosamino)-1-(3-pyridyl)-
 - Tobacco Alkaloids, Review, 79-5414
- Dipropylamine, 2,2'-Dihydroxy-N-nitroso-
 - Carcinogenic Potential, 79-5564
- Dipropylamine, 2,2'-Dioxo-N-nitroso-
 - Carcinogenic Potential, 79-5564
- Nicotine, 1'-Demethyl-1'-nitroso-
 - Tobacco Alkaloids, Review, 79-5414
- Pyrrolidine, 1-Nitroso-
 - Tobacco Alkaloids, Review, 79-5414

Retinoblastoma

- Child
 - Epidemiology, Sweden, 79-5928
- Chromosomes, Human, 21-22
 - Chromosomes, Human, 13-15, 79-5476
- Genetics, Review
 - Chromosomes, Human, 13-15, 79-5476
- Radiation, Ionizing
 - Chromosomes, Review, 79-5444

Retinoic Acid

- Prostate
 - Metaplasia, 79-5644
- Prostatic Hypertrophy
 - Cholanthrene, 3-Methyl-, 79-5644
- 12- α -Tetradecanoylphorbol-13-acetate
 - Metabolism, Lymphocytes, 79-5623

13-cis-Retinoic Acid

- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-79-5643

Retinol

- Cervix Neoplasms
 - Diet, 79-5965
- Lung Neoplasms
 - Smoking, 79-5965

Retinol Palmitate

- Mouth Neoplasms
 - Calcium Oxide, 79-5535
 - Hyperplasia, 79-5535
 - Keratinosis, 79-5535
 - Tobacco, 79-5535

Retroperitoneal Fibrosis

- Case Report
 - Child, 79-5883

Reverse Transcriptase

- Benzo(a)pyrene
 - Virus, Rauscher Murine Leukemia
 - 79-5753
- Leukemia
 - Precancerous Conditions, 79-5765
- Leukemia, Myelocytic
 - Shay Tumor, 79-5982
- Myelofibrosis
 - Isolation and Characterization
 - 79-5765
- Virus, Abelson Murine Leukemia
 - Fibroblasts, 79-5737
 - Lymphocytes, 79-5737
 - Viral Proteins, 79-5737
- Virus, Avian Myeloblastosis
 - Endonucleases, 79-5705
- Virus, Gibbon Ape Lymphoma
 - Antibody Specificity, 79-5765
- Virus, Kirsten Murine Leukemia
 - DNA, Viral, 79-5750
- Virus, Kirsten Murine Sarcoma
 - DNA, Viral, 79-5750
- Virus, Moloney Murine Leukemia
 - DNA, Viral, 79-5750
- Virus, Moloney Murine Sarcoma
 - Protein Kinase, 79-5751
- Virus, Murine Mammary Tumor
 - Transmission, Review, 79-5458
- Virus, Rauscher Murine Leukemia
 - DNA, Viral, 79-5750
- Virus, Simian Sarcoma

Reverse Transcriptase (cont'd)
Antibody Specificity, 79-5765

Rhabdomyosarcoma

Formamide, *N,N*-Dimethyl-
Cell Differentiation, 79-5999
Virus, C-Type RNA Tumor
Isolation and Characterization, Snake
79-5757
Virus, Mason-Pfizer Monkey
Virus Replication, 79-5766

RNA, Messenger

Cycloheximide
Alpha Globulins, 79-5544
Diethylamine, *N*-Nitroso-
Polyribosomes, 79-5562
Extrachromosomal Inheritance
DNA, 79-5716
Procollagen, 79-5716
Methanol, (Methyl-*ONN*-azoxy)-, Ace-
tate (Ester)
Polyribosomes, 79-5517
Virus, Adeno 5
HeLa Cells, 79-5813, 79-5814
Host Range Mutants, 79-5813
Nucleic Acid Precursors, 79-5813
Virus, Epstein-Barr
DNA, Viral, 79-5779
Virus, Herpes Simplex 1
Cycloheximide, 79-5770
DNA, Viral, 79-5770
Virus, Polyoma
DNA Replication, 79-5786
Nucleic Acid Homology, 79-5788
Virus, Polyoma, BK
Cell Transformation, Neoplastic
79-5789
Nucleotide Sequence, 79-5789
Virus, Rous Sarcoma
Procollagen, 79-5712, 79-5716
Virus, SV40
Adenosine, *N*-Methyl-, 79-5796
Adenosine Triphosphate, 79-5795
DNA, Viral, 79-5793
Nucleotide Sequence, 79-5789
79-5795
Xenopus laevis
Interferon, 79-5976
Milk Proteins, 79-5976

RNA Polymerase

Virus, Reo 3
Radiation, Ionizing, 79-5687
Virus, SV40
DNA, Viral, 79-5794, 79-5795

RNA Replicase

Virus, Polio
HeLa Cells, 79-5822

RNA Replication

Virus, Adeno 2
Benzimidazole, 5,6-Dichloro-1- β -*D*-
ribofuranosyl-, 79-5811

RNA, Ribosomal

Aflatoxin B1
Nucleic Acids, Binding, 79-5620
Aflatoxin G1
Nucleic Acids, Binding, 79-5620

RNA, Transfer

Benzidine, *N*-Hydroxy-*N,N'*-diacetyl-
Binding, 79-5615
Virus, Moloney Murine Leukemia
DNA Replication, 79-5752
Nucleotide Sequence, 79-5752

RNA, Viral

Virus, Adeno 2
HeLa Cells, 79-5811
Nucleotide Sequence, 79-5811
Virus, Adeno 5
DNA-RNA Hybridization, 79-5814
Temperature Sensitive Mutants
79-5814
Virus, Friend Spleen Focus-Forming
Nucleotide Sequence, 79-5740

RNA, Viral (cont'd)

Virus, Helper, 79-5740
Virus, Moloney Murine Leukemia
DNA Replication, 79-5752
Virus, Murine Mammary Tumor
Strain Difference, 79-5733
Virus, Rous Sarcoma
DNA-RNA Hybridization, 79-5717
Isolation and Characterization
79-5717
Virus, SV40
Adenosine, *N*-Methyl-, 79-5796

Ro 10-9359

Skin Neoplasms
12-*O*-Tetradecanoylphorbol-13-acetate
79-5633

Saccharomyces cerevisiae

1,2-Benzisothiazolin-3-one, 1,1-Dioxide
Mutagenic Activity, 79-5613
Carcinogen, Chemical
Cytochromes, 79-5514
Mitochondria, 79-5514
Mutagenic Activity, 79-5514

Salmonella typhimurium

Nitrous Acid, Sodium Salt
Mutation, 79-5557

Sarcoidosis

Lymphoma
Case Report, 79-5861

Sarcoma

Antigenic Determinants
Antibody Specificity, 79-5835
Bone Neoplasms
Radiation, Ionizing, 79-5449
Cholanthrene, 3-Methyl-
Antibody Specificity, 79-5835
Neoplasm Transplantation, 79-5641
Neoplasm Metastasis
Lymph Nodes, Review, 79-5479
Surface Properties
Ascitic Tumor, 79-5641
Virus, Adeno 2
Antigens, Neoplasm, 79-5808
Virus, Adeno 12
Antigens, Neoplasm, 79-5808
Virus, Feline Sarcoma
Graft Rejection, 79-5837
Virus, Rous Sarcoma
DNA-RNA Hybridization, 79-5711
Histocompatibility Antigens, 79-5702
Virus, SV40
Histocompatibility Antigens, 79-5836
Transplantation Immunology, 79-5836
Wounds and Injuries
Case Report, 79-5885
Neoplasm Recurrence, Local, 79-5885
Xanthine, 3-Hydroxy-
Structure-Activity Relationship
79-5594

Sarcoma, Granulocytic

see Leukemia, Myelocytic

Sarcoma, Jensen

Cholanthrene, 3-Methyl-
Immune Response, Rat, 79-5639

Sarcoma, Mast Cell

Growth
Electroshock, 79-5987
Stress
Growth, 79-5987

Sarcoma, Osteogenic

Guanidine, 1-Methyl-3-nitro-1-nitroso-
Cycloheximide, 79-5746
Neoplasms, Radiation-Induced
Virus, C-Type RNA Tumor, 79-5693
Radiation, Ionizing
Epidemiology, Review, 79-5449
Radium
Dose-Response Study, Dog, 79-5678
Virus-Like Particles, 79-5693
Strontium
Dose-Response Study, Dog, 79-5678

Sarcoma, Osteogenic (cont'd)

Yttrium Radioisotopes, 79-5678
Thorium
Virus-Like Particles, 79-5693
Virus, Kirsten Murine Sarcoma
Cycloheximide, 79-5746
Virus, Polyoma, BK
Carcinogenic Potential, Hamster
79-5791

Sarcoma, Reticulum Cell

Benzene
Occupational Hazard, 79-5932
Colonic Neoplasms
Case Report, 79-5907
Genetics
Case Report, 79-5854
Kidney Transplantation
Case Report, 79-5846
Leukemia, Myelocytic
Eosinophils, 79-5856

Scleroderma, Systemic

Esophageal Neoplasms
Carcinoma, Epidermoid, 79-5894
Case Report, 79-5894

Sebaceous Gland Neoplasms

Acetic Acid, Methylnitrosaminomethyl
Ester
Zymbal Gland, 79-5550

4,8-Secosenecionan-8,11,16-trione, 12-

Hydroxy-4-methyl-
Hepatoma
Carcinogenic Activity, Rat, 79-5572

Selenium

Carcinogen, Chemical
Metabolism, Review, 79-5405
Glutathione Peroxidase
Antineoplastic Activity, Review
79-5405

Senkirkine

see 4,8-Secosenecionan-8,11,16-trione,
12-Hydroxy-4-methyl-

Siderosis

Lung Neoplasms
Case Report, 79-5892

Skin Diseases

Genetics
DNA Repair, 79-5692

Skin Neoplasms

Carcinoma, Basal Cell
Arsenic, 79-5534
Leukemia, Myelocytic
Case Report, 79-5857
Lymphomatoid Papulosis
Case Report, 79-5860
Nevus, Pigmented
Epidemiology, Review, 79-5480
Papilloma
Benz(a)anthracene, 7,12-Dimethyl-
79-5632, 79-5633
Nucleotides, Cyclic, 79-5632
Psoralen, 8-Methoxy-
Photochemotherapy, Review, 79-5447
12-*O*-Tetradecanoylphorbol-13-acetate
Fluocinolone Acetonide, 79-5633
Ro 10-9359, 79-5633
Ultraviolet Rays
Age Factors, Review, 79-5446
Photochemotherapy, Review, 79-5447

Sminthopsis crassicaudata

Virus-Like Particles
A-Type Particles, 79-5819

Smoking

Aryl Hydrocarbon Hydroxylases
Microsomes, Liver, 79-5518
Benzo(a)pyrene, 7,8-Dihydro-9,10-oxy-
7,8,9,10-tetrahydro-
DNA Adduct, 79-5661
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-5910

Smoking (cont'd)

- Neoplasms, Multiple Primary, 79-5970
- Cysteine, *N*-Acetyl-
Thioethers, 79-5580
- Digestive System Neoplasms
- Ethyl Alcohol, 79-5965
- Laryngeal Neoplasms
- Epidemiology, 79-5888
- Ethyl Alcohol, 79-5889
- Neoplasm Metastasis, 79-5889
- Precancerous Conditions, 79-5889
- Lung Neoplasms
- Adenocarcinoma, 79-5963
- Blacks, Review, 79-5495
- Carcinoma, 79-5963
- Carcinoma, Bronchiolar, 79-5963
- Carcinoma, Epidermoid, 79-5963
- Epidemiology, 79-5940
- Retinol, 79-5965
- Neoplasms
- Epidemiology, Review, 79-5496
- Urine
- Ames Test, 79-5580
- Mutagens, 79-5580

Sodium Azide

- Ames Test
- Carcinogenic Potential, Review
- 79-5406

Soft Tissue Neoplasms

- Liver Neoplasms
- Dog, Review, 79-5434
- Water, Heavy
- Carcinogenic Activity, Rat, 79-5676

Somatotropin

- Adenoma
- Ergocryptine, 2-Bromo-, 79-5595
- Theophylline, 79-5595
- Thyrotropin Releasing Hormone
- 79-5595
- Pituitary Neoplasms
- Adenoma, 79-5595

Somatotropin Release Inhibiting Hormone

- Gastrointestinal Neoplasms
- Neoplastic Endocrine-Like Syndromes
- 79-5483

Spermatozoa

- Carcinogen, Chemical
- Morphology, Review, 79-5421
- Ethane, 1,2-Dibromo-
Abnormalities, 79-5521
- Chromatin, 79-5521
- Teratogenic Effect, 79-5522
- Genetics
- Abnormalities, Review, 79-5421
- Radiation, Ionizing
- Morphology, Review, 79-5421

4,4'-Stilbenediol, α,α' -Diethyl-

- Abnormalities
- Urogenital System, Rat, 79-5667
- Cryptorchism
- Testicular Hypoplasia, 79-5671
- Estradiol
- Receptors, Hormone, 79-5637
- Gynecologic Neoplasms
- Transplacental, Transmammary Carcinogenesis, 79-5667
- Lymphocytes
- Concanavalin A, 79-5670
- Lipopolysaccharides, 79-5670
- Mitogens
- Immune Response, Mouse, 79-5670
- Receptors, Hormone
- Estrogen Agonists, Review, 79-5438
- Vaginal Neoplasms
- Precancerous Conditions, 79-5668
- 79-5669
- Transplacental Carcinogenesis, Review
- 79-5437

Stomach Neoplasms

- Adenocarcinoma
- Guanidine, 1-Propyl-3-nitro-1-nitroso-
79-5591

Stomach Neoplasms (cont'd)

- Hermans' Syndrome, 79-5842
- Adenoma
- Guanidine, 1-Propyl-3-nitro-1-nitroso-
79-5591
- Carcinoma
- Precancerous Conditions, 79-5504
- Cimetidine
- Glycoproteins, 79-5416
- Nitroso Derivative, Review, 79-5415
- 79-5416
- Dysgammaglobulinemia
- Case Report, 79-5842
- Epidemiology
- France, 79-5968
- Gastrectomy
- Diagnosis, Review, 79-5488
- Epidemiology, Review, 79-5484
- Precancerous Conditions, 79-5488
- Gastric Mucosa
- Immunoglobulins, 79-5841
- Gastritis
- Epidemiology, Japan, 79-5504
- Precancerous Conditions, Review
- 79-5484
- Genetics
- Case Report, 79-5899
- Granuloma
- Polyps, 79-5896
- IgA
- Secretory Component, 79-5841
- Leiomyoma
- Polyps, 79-5896
- Lipoma
- Polyps, 79-5896
- Metaplasia
- Epidemiology, Japan, 79-5504
- Guanidine, 1-Propyl-3-nitro-1-nitroso-
79-5591
- Neurilemmoma
- Case Report, 79-5900
- Papilloma
- Urea, 3,3-Bis(2-chloroethyl)-1-methyl-
1-nitroso-, 79-5571
- Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-
nitroso-, 79-5571
- Urea, 1-(2-Chloroethyl)-3,3-dimethyl-
1-nitroso-, 79-5571
- Urea, 1,3,3-Tris(2-chloroethyl)-1-
nitroso-, 79-5571
- Peptic Ulcer
- Precancerous Conditions, Review
- 79-5484
- Pyloric Stenosis
- Case Report, 79-5900

Stress

- Sarcoma, Mast Cell
- Growth, 79-5987

Strontium

- Myeloproliferative Disorders
- Dose-Response Study, Dog, 79-5678
- Nose Neoplasms
- Carcinoma, Epidermoid, 79-5684
- Radioactive Fallout
- Greenland, 79-5927
- Sarcoma, Osteogenic
- Dose-Response Study, Dog, 79-5678
- Yttrium Radioisotopes, 79-5678

Styrene

- Aryl Hydrocarbon Hydroxylases
- Microsomes, Liver, 79-5609
- Benzo(a)pyrene
- Ames Test, 79-5609
- Epoxide Hydratases
- Microsomes, Liver, 79-5609
- Maleic Acid, Diethyl Ester
- Ames Test, 79-5608
- Propane, 1,2-Epoxy-3,3,3-trichloro-
Ames Test, 79-5608

Sucrase

- Teratoid Tumor
- Rosette Formation, 79-5989

Sulphydryl Compounds

- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Intestinal Mucosa, 79-5604

Sulfuric Acid, Nickel Salt

- Virus, Simian Adeno 7
- DNA, Viral, 79-5640

Sulfurous Acid, Monosodium Salt

- Barley
- Mutagenic Activity, 79-5543

Surface Properties

- Carcinoma, Epidermoid
- Ascitic Tumor, 79-5641
- Sarcoma
- Ascitic Tumor, 79-5641

Surgery, Operative

- Colonic Neoplasms
- Immunity, Cellular, 79-5547
- Eye Neoplasms
- Neoplasm Recurrence, Local, 79-5875

Symphytine

- Hepatoma
- Plant Extracts, 79-5572

Teratoid Tumor

- Alpha Fetoproteins
- Diagnosis and Prognosis, Review
- 79-5465

Carbohydrates

- Cell Adhesion, 79-5989
- Cell Membrane, 79-5989
- Cholesterol
- Metabolism, 79-5988
- Collagen
- Amino Acids, 79-5990
- Basement Membrane, 79-5990
- Cell Differentiation, 79-5990
- Peptides, 79-5990
- Cyanogen Bromide
- Collagen, 79-5990

Lipoproteins

- Receptors, LDL, 79-5988
- Neoplasm Metastasis
- Peritoneum, 79-5919
- Ovarian Neoplasms
- Neoplasm Metastasis, 79-5919
- Ultrastructural Study, 79-5919
- Peroxidases
- Rosette Formation, 79-5989
- Polysaccharides
- Rosette Formation, 79-5989
- Sucrase
- Rosette Formation, 79-5989
- Testicular Neoplasms
- Case Report, 79-5924

Testicular Neoplasms

- Cryptorchism, Review
- Gonadal Dysgenesis, 79-5487
- Disgerminoma
- Acetophenone, 2-Amino-, 79-5673
- Teratoid Tumor
- Case Report, 79-5924

Testosterone

- Adrenal Gland Neoplasms
- Adenoma, 79-5666

12-*O*-Tetradecanoylphorbol-13-acetate

- Alanine, 2-Methyl-
Metabolism, Lymphocytes, 79-5623
- Catecholamines
- Adenosine Cyclic 3',5' Monophosphate, 79-5625
- 5,8,11,14-Eicosatetraenoic Acid
- Metabolism, Fibroblasts, 79-5624
- Epidermal Growth Factors
- Binding Sites, 79-5622
- Prostaglandins E
- Adenosine Cyclic 3',5' Monophosphate, 79-5625
- Metabolism, Fibroblasts, 79-5624
- Retinoic Acid
- Metabolism, Lymphocytes, 79-5623
- Skin Neoplasms
- Fluocinolone Acetonide, 79-5633

12-O-Tetradecanoylphorbol-13-acetate

(cont'd)

Ro 10-9359, 79-5633

Virus, Adeno 5

Cell Transformation, Neoplastic
79-5815

Virus, Epstein-Barr

Co-carcinogenic Effect, 79-5626

Theophylline

Adenoma

Prolactin, 79-5595

Somatotropin, 79-5595

Breast Diseases

Adenofibroma, 79-5596

Cysts, 79-5596

Nucleotides, Cyclic, 79-5596

Thio-TEPA

see Phosphine Sulfide, Tris(1-aziridinyl)-

Thorium

Sarcoma, Osteogenic

Virus-Like Particles, 79-5693

Thorium Dioxide

Angiosarcoma

Epidemiology, Review, 79-5436

Thymidine Kinase

Hepatoma

Dexamethasone, 79-5704

Virus, Avian Leukosis, 79-5703

Thymine

Radiation, Ionizing

Mutagenic Derivative, 79-5581

Ultraviolet Rays

Mutagenic Derivative, 79-5581

Thymine, 5,6-Dihydro-6-hydroperoxy-5-hydroxy-

Ames Test

Mutagenic Activity, 79-5581

Virus, Influenza

DNA, Viral, 79-5581

Thymine Nucleotides

Plasmacytoma

DNA Polymerase, 79-5986

Thymus Gland

Histocompatibility Antigens

Graft vs Host Reaction, Review
79-5462

T-Lymphocytes

Transplantation, Review, 79-5462

Lymphocyte Cooperation

Transplantation, Review, 79-5462

Thymus Neoplasms

Lymphoma

Benz(a)anthracene, 7,12-Dimethyl-
79-5728

Thyroid Neoplasms

Adenomatosis, Familial Endocrine

Case Report, 79-5870

Carcinoma

Neoplastic Endocrine-Like Syndromes
79-5868

Dipropylamine, 2,2'-Dioxo-N-nitroso-
Histological Study, Rat, 79-5564

Endrin

Dog, Review, 79-5434

Hypercalcemia

Neoplastic Endocrine-Like Syndromes
79-5868

Thyrotropin Releasing Hormone

Adenoma

Prolactin, 79-5595

Somatotropin, 79-5595

Tobacco

Mouth Neoplasms

Retinol Palmitate, 79-5535

Uranium

Contaminant Levels, 79-5694

p-Tolualdehyde

see Benzaldehyde, 4-Methyl-

p-Toluamide, N-Isopropyl- α -(2-methylhydrazino)-, HCl

Leukemia, Lymphocytic

Lymphosarcoma, 79-5930

p-Toluamide, N-Isopropyl- α -(2-methylhydrazino)-

Ames Test

Mutagenic Activity, 79-5606

DNA Repair

Arabinose Resistance, 79-5606

Granuloma

Methanesulfonic Acid, Methyl Ester
79-5577

Toluene

Chick Embryo

Teratogenic Effect, 79-5523

Chromatids

Lymphocytes, 79-5605

Hyperplasia

Benzo(a)pyrene, 79-5654

Leukemia, Myelocytic

Carcinogenic Potential, Review

79-5418

Myelofibrosis

Carcinogenic Potential, Review

79-5418

Occupational Hazard

Chromosome Aberrations, 79-5605

Metabolism, Review, 79-5418

Tongue Neoplasms

Papilloma

Benz(a)anthracene, 7,12-Dimethyl-
79-5685

Radiation, Ionizing, 79-5685

Radiation, Ionizing

Co-carcinogenic Effect, 79-5685

Toxins

Hepatoma

Ground Nuts, 79-5960

Jaundice

Food Contamination, 79-5960

Tracheal Neoplasms

Carcinoma, Epidermoid

Arsenic, 79-5534

Transfection

Virus, Murine Sarcoma

Transformation, Genetic, 79-5708

Transformation, Genetic

Agrobacterium tumefaciens

Methanesulfonic Acid, Methyl Ester

79-5576

Ultraviolet Rays, 79-5576

Virus, Murine Sarcoma

Transfection, 79-5708

Virus, Rous Sarcoma

DNA, Viral, 79-5708

Virus, SV40

Bacteriophages, 79-5799

DNA, Viral, 79-5799, 79-5800

Transplantation

Gastrointestinal Neoplasms

Plasmacytoma, 79-5908

Transplantation, Heterologous

Adenocarcinoma

Petroleum, 79-5832

Polycythemia, 79-5914

Cell Transformation, Neoplastic

Mouse, Nude, Review, 79-5470

Leukocytes

Cell Transformation, Neoplastic

79-5826

Fetal Blood, 79-5826

Lung Neoplasms

Adenocarcinoma, 79-5914

Lymphoma

Virus, Epstein-Barr, 79-5783

Melanoma

Chromosome Abnormalities, 79-5991

Transplantation, Heterologous (cont'd)

DOPA Oxidase, 79-5879

Growth, 79-5991

Mouse, Nude, 79-5991

Neoplasms

Mouse, Nude, Review, 79-5469

79-5472

Plasmacytoma

Petroleum, 79-5832

Virus Activation

Mouse, Nude, Review, 79-5469

Transplantation, Homologous

Mammary Neoplasms, Experimental

Fetal Mesenchyma, 79-5732

Mouth Neoplasms

Antilymphocyte Serum, 79-5630

Neoplasm Invasiveness, 79-5630

Transplantation Immunology

Hepatoma

Lymphocytes, 79-5704

Virus, Avian Leukosis, 79-5704

Plasmacytoma

Petroleum, 79-5832

Sarcoma

Virus, SV40, 79-5836

Virus, Gross Murine Leukemia

T-Lymphocytes, 79-5744

Virus, Murine Leukemia

Antigens, Viral, 79-5725

Triazene, 1-Methyl-3-phenyl-

Guanine, 7-Methyl-

Nucleic Acids, Alkylation, 79-5584

Purine, 2-Amino-6-methoxy-

Brain, Rat, 79-5584

s-Triazine, 2,4,6-Tris(1-aziridinyl)-

Mutagenic Activity

Dominant Lethal Test, 79-5583

Strain Differences, Rat, 79-5583

Trophoblastic Tumor

Chromosome Aberrations

Drug Therapy, 79-5512

Radiotherapy, 79-5512

Tuberculin

Breast Neoplasms

Hypersensitivity, Delayed, 79-5849

Neoplasms

Hypersensitivity, Delayed, 79-5838

Tuberculosis, Pulmonary

Plant Agglutinins

Reaction, Cutaneous, 79-5845

Tubericidin

Adenosine Triphosphate

Erythrocytes, 79-5977

Lactic Acid

Erythrocytes, 79-5977

Tubulin

Virus, Murine Sarcoma

Protein Kinase, 79-5729

Tyrosine Aminotransferase

Hepatoma

Dexamethasone, 79-5704

Glucagon, 79-5704

UDP Glucuronosyltransferase

Barbituric Acid, 5-Ethyl-5-phenyl-

Microsomes, 79-5532

Cholanthrene, 3-Methyl-

Microsomes, 79-5532

Ultrasonics

Pancreatic Neoplasms

Diagnosis, Review, 79-5501

Radiotherapy

Carcinogenic Potential, Review

79-5451

Ultraviolet Rays

Acetamide, N-Fluorenyl-2-yl-

Endonucleases, 79-5628

Agrobacterium tumefaciens

Transformation, Genetic, 79-5576

Ultraviolet Rays (cont'd)

- Caffeine
 - DNA Photolyase, 79-5688
- Chromosome Aberrations
 - Cell Survival, 79-5680
 - Mitosis, 79-5680
- Endonucleases
 - DNA Repair, 79-5628
- Fibrosarcoma
 - Immunity, Cellular, 79-5834
- Mutation
 - Fibroblasts, Review, 79-5448
- Mycosis Fungoides
 - Hypersensitivity, 79-5933
- Psoralen, 4,5',8-Trimethyl-
 - Chromatids, 79-5692
 - DNA Adducts, 79-5692
- Skin Neoplasms
 - Age Factors, Review, 79-5446
 - Photochemotherapy, Review, 79-5447
- Thymine
 - Mutagenic Derivative, 79-5581
- Virus, Herpes Simplex 2
 - Cell Transformation, Neoplastic 79-5773, 79-5775
 - Cellular Inclusions, 79-5774
 - Virus Replication, 79-5774
- Virus, Rous Sarcoma
 - Deletion Mutants, 79-5713
 - DNA, Viral, 79-5713
- Xeroderma Pigmentosum
 - Chromatids, 79-5680
 - DNA Repair, Review, 79-5448

- Uracil, 5-(Bis(2-chloroethyl)amino)-**
 - Antineoplastic Agents
 - Guanyl Cyclase, 79-5590
 - Guanidine, 1-Propyl-3-nitro-1-nitroso-
 - Guanyl Cyclase, 79-5590
 - Hydrazine
 - Guanyl Cyclase, 79-5590

- Uracil, 5-Hydroperoxymethyl-**
 - Ames Test
 - Mutagenic Activity, 79-5581
 - Virus, Influenza
 - DNA, Viral, 79-5581

- Uranium**
 - Lung Neoplasms
 - Epidemiology, 79-5690
 - Histological Study, 79-5690
 - Tobacco
 - Contaminant Levels, 79-5694

- Urea, 3,3-Bis(2-chloroethyl)-1-methyl-1-nitroso-**
 - Esophageal Neoplasms
 - Papilloma, 79-5571
 - Lung Neoplasms
 - Carcinoma, Epidermoid, 79-5571
 - Stomach Neoplasms
 - Papilloma, 79-5571

- Urea, 1-(2-Chloroethyl)-3,3-diethyl-1-nitroso-**
 - Lung Neoplasms
 - Adenoma, 79-5571
 - Carcinoma, Epidermoid, 79-5571
 - Stomach Neoplasms
 - Papilloma, 79-5571

- Urea, 1-(2-Chloroethyl)-3,3-dimethyl-1-nitroso-**
 - Esophageal Neoplasms
 - Papilloma, 79-5571
 - Lung Neoplasms
 - Adenoma, 79-5571
 - Stomach Neoplasms
 - Papilloma, 79-5571

- Urea, Ethyl Nitroso-**
 - Cell Transformation, Neoplastic
 - Brain, Fetal Rat, 79-5569
 - Ultrastructural Study, 79-5569
 - DNA
 - Hydrogen Bonding, 79-5568
 - Lung Neoplasms
 - Adenoma, 79-5891

- Urea, Ethyl Nitroso- (cont'd)**
 - Transplacental Carcinogenesis 79-5891

- Nervous System Neoplasms**
 - Transplacental Carcinogenesis 79-5570

- Neurilemmoma**
 - Ultrastructural Study, 79-5925

- Nitrogen**
 - Hydrogen Bonding, 79-5568

- Oxygen**
 - Hydrogen Bonding, 79-5568

- Polynucleotides**
 - Alkylation, 79-5568
- Xeroderma Pigmentosum**
 - DNA, Alkylation, 79-5993

- Urea, Methyl Nitroso-**
 - Brain Neoplasms
 - Astrocytoma, 79-5566
 - Glioma, 79-5566
 - Oligodendroglioma, 79-5566
 - Chromosome Aberrations
 - Lymphocytes, 79-5575
 - DNA Repair
 - Adenine, 3-Methyl-, 79-5567
 - Guanine, 7-Methyl-, 79-5567
 - Hamster V79 Cells, 79-5567
 - Purine, 2-Amino-6-methoxy-, 79-5567
 - Spermatids, Mouse, 79-5565
 - Glioma
 - Estrogens, 79-5925
 - Ultrastructural Study, 79-5925
 - Purine, 2-Amino-6-methoxy-
 - DNA Repair, 79-5579

- Urea, 1,3,3-Tris(2-chloroethyl)-1-nitroso-**
 - Lung Neoplasms
 - Adenoma, 79-5571
 - Stomach Neoplasms
 - Papilloma, 79-5571

- Uridine, 5-Bromo-2'-deoxy-**
 - Virus, Murine Leukemia
 - Virus Activation, 79-5727

- Uridine, 2'-Deoxy-5-iodo-**
 - Virus, Epstein-Barr
 - Virus Activation, 79-5781
 - Virus, Marek's Disease Herpes
 - Macrophages, 79-5723
 - Virus, Murine Leukemia
 - Virus Activation, 79-5727

- Uridine Diphosphate Glucuronic Acid**
 - Benzo(a)pyren-1-ol
 - Mutagenic Metabolite, 79-5649
 - Benzo(a)pyren-3-ol
 - DNA, Binding, 79-5653
 - Mutagenic Metabolite, 79-5649
 - Benzo(a)pyren-9-ol
 - DNA, Binding, 79-5653

- Urine**
 - Smoking
 - Ames Test, 79-5580
 - Mutagens, 79-5580

- Urogenital Neoplasms**
 - Carcinogen, Chemical
 - DNA Repair, Review, 79-5420
 - Carcinoma, Epidermoid
 - Dipropylamine, 2,2'-Dioxo-N-nitroso- 79-5564
 - Dipropylamine, 2,2'-Dioxo-N-nitroso-
 - Histological Study, Rat, 79-5564
 - Oncogenic Viruses
 - Co-carcinogenic Effect, Review 79-5420
 - Radiation, Ionizing
 - DNA Repair, Review, 79-5420

- Uterine Neoplasms**
 - Diabetes Mellitus
 - Pituitary Hormones, Review, 79-5485
 - Estrogens
 - Epidemiology, 79-5929
 - Epidemiology, Review, 79-5439
 - Menopause, 79-5929, 79-5949

Uterine Neoplasms (cont'd)

- Geographic Factors**
 - Epidemiology, 79-5948
- Progestational Hormones**
 - Epidemiology, Review, 79-5439

Vaginal Neoplasms

- Estradiol, 3-Benzozate**
 - Histological Study, Mouse, 79-5669
- Precancerous Conditions, 79-5669**
 - 4,4'-Stilbenediol, α,α' -Diethyl-
 - Precancerous Conditions, 79-5668
- Transplacental Carcinogenesis, Review 79-5437**

Vasculitis

- Nervous System Neoplasms**
 - Adrenal Cortex Hormones, 79-5863
- Lymphoma, 79-5863**

Vinblastine

- Leukemia, Lymphocytic**
 - Lymphosarcoma, 79-5930

Vincristine

- Leukemia, Lymphocytic**
 - Lymphosarcoma, 79-5930

Viral Proteins

- Virus, Abelson Murine Leukemia**
 - Reverse Transcriptase, 79-5737
 - Virus, Helper, 79-5760
- Virus, Adeno 2**
 - Host Range Mutants, 79-5809
- Virus, Adeno 5**
 - Host Range Mutants, 79-5809
- Virus, Bovine Leukemia**
 - Amino Acids, 79-5763
- Virus, Feline Sarcoma**
 - Virus, Helper, 79-5760
- Virus, Friend Spleen Focus-Forming**
 - Immunoprecipitation, 79-5739
- Virus, Mink Cell Focus-Inducing**
 - Virus, Helper, 79-5760
- Virus, Murine Mammary Tumor**
 - Isolation and Characterization 79-5730
 - Peptides, 79-5730
- Virus, SV40**
 - Chromatin, 79-5802
 - Nuclear Morphology, 79-5792

Viral Vaccines

- Virus Cultivation**
 - Carcinogenic Potential, 79-5454
 - Cell Substrate, Review, 79-5454

Virus, Abelson Murine Leukemia

- Antigenic Determinants**
 - Cell Transformation, Neoplastic 79-5760
- Reverse Transcriptase**
 - Fibroblasts, 79-5737
 - Lymphocytes, 79-5737
 - Viral Proteins, 79-5737
- Viral Proteins**
 - Virus, Helper, 79-5760
- Virus, Helper**
 - Cell Transformation, Neoplastic 79-5737

Virus Activation

- Virus, Epstein-Barr**
 - Chromosomes, 79-5781
- Uridine, 2'-Deoxy-5-iodo-, 79-5781**
- Virus, Kirsten Murine Sarcoma**
 - Cycloheximide, 79-5747
- Imidazole-1-ethanol, 2-Methyl-5-nitro 79-5747**
 - Protease Inhibitors, 79-5747
- Virus, Murine Leukemia**
 - Uridine, 5-Bromo-2'-deoxy-, 79-5727
 - Uridine, 2'-Deoxy-5-iodo-, 79-5727
- Virus, Reo 3**
 - Radiation, Ionizing, 79-5687

- Virus, Adeno 2**
 - Benzimidazole, 5,6-Dichloro-1- β -D-ribofuranosyl-

- Virus, Adeno 2 (cont'd)**
 RNA Replication, 79-5811
 DNA, Viral
 Carrier Proteins, 79-5809
 Deletion Mutants, 79-5810
 Mutation, 79-5809
 Virus, Helper, 79-5810
 RNA, Viral
 HeLa Cells, 79-5811
 Nucleotide Sequence, 79-5811
 Sarcoma
 Antigens, Neoplasm, 79-5808
 Viral Proteins
 Host Range Mutants, 79-5809
 Virus Replication
 Morphological Revertants, 79-5818
- Virus, Adeno 4**
 Lysosomes
 HeLa Cells, 79-5812
 Virus Replication, 79-5812
- Virus, Adeno 5**
 Cell Transformation, Neoplastic
 Temperature Sensitive Mutants
 79-5815
 DNA, Viral
 Carrier Proteins, 79-5809
 Mutation, 79-5809
 RNA, Messenger
 HeLa Cells, 79-5813, 79-5814
 Host Range Mutants, 79-5813
 Nucleic Acid Precursors, 79-5813
 RNA, Viral
 DNA-RNA Hybridization, 79-5814
 Temperature Sensitive Mutants
 79-5814
 12-*O*-Tetradecanoylphorbol-13-acetate
 Cell Transformation, Neoplastic
 79-5815
 Viral Proteins
 Host Range Mutants, 79-5809
 Virus, Herpes Simplex 1
 Viral Interference, 79-5772
 Virus Replication, 79-5772
 Virus Replication
 Cell Transformation, Neoplastic
 79-5772
- Virus, Adeno 7**
 DNA, Viral
 Cleavage Sites, 79-5816
 Endonucleases, 79-5816
 Neoplasms
 DNA-DNA Hybridization, 79-5817
 Neoplasms, Experimental
 DNA, Viral, 79-5817
- Virus, Adeno 11**
 Neoplasms
 DNA-DNA Hybridization, 79-5817
- Virus, Adeno 12**
 DNA, Viral
 Morphological Revertants, 79-5818
 Sarcoma
 Antigens, Neoplasm, 79-5808
- Virus, Adeno 31**
 Lysosomes
 HeLa Cells, 79-5812
 Virus Replication, 79-5812
- Virus, Adeno 2 · SV40 Hybrid**
 DNA Replication
 Clone Cells, 79-5810
- Virus, AKR Murine Leukemia**
 Antigens, Viral
 Immunity, Cellular, 79-5744
 Genetics
 Immune Response, Review, 79-5455
 Glycopeptides
 Isolation and Characterization
 79-5755
 T-Lymphocytes
 Suppressor Cells, Review, 79-5455
 Lymphoma
 Immunity, Cellular, Review, 79-5455
- Virus, Avian Leukemia**
 Chick Embryo
 Complement Fixation Tests, 79-5698
- Virus, Avian Leukosis**
 Antigens, Viral
 Crosses, Genetic, 79-5699
 DNA, Viral
 Crosses, Genetic, 79-5699
 Hepatoma
 BCG, 79-5704
 Chromatin, 79-5700
 DNA, 79-5700
 Glucosephosphate Dehydrogenase
 79-5703
 Histocompatibility Antigens, 79-5702
 Neoplasm Transplantation, 79-5701
 Thymidine Kinase, 79-5703
 Transplantation Immunology, 79-5704
 Ultrastructural Study, 79-5701
 Xanthine Oxidase, 79-5703
 Lymphocyte Transformation
 Antigenic Determinants, 79-5825
 T-Lymphocytes
 Immunity, Cellular, 79-5825
 Virus, Rous Sarcoma
 Antigenic Determinants, 79-5702
- Virus, Avian Myeloblastosis**
 Endonucleases
 DNA, Superhelical, 79-5705
 Reverse Transcriptase, 79-5705
 Glycoproteins
 Hexoses, 79-5706
 Lactic Acid, 79-5706
 Lymphocyte Transformation
 Antigenic Determinants, 79-5825
 T-Lymphocytes
 Immunity, Cellular, 79-5825
- Virus, Avian Reticuloendotheliosis**
 Cells, Cultured
 Tumorigenicity, 79-5719
 B-Lymphocytes
 Antigen-Antibody Reactions, 79-5719
 Cell Transformation, Neoplastic
 79-5719
- Virus, Avian Sarcoma**
 DNA, Viral
 Viral Interference, 79-5710
 Phosphoproteins
 Cell Transformation, Neoplastic
 79-5707
 Protein Kinase, 79-5707
 Virus Replication
 Transformation Defective Mutants
 79-5710
- Virus, Baboon**
 Immune Serums
 Neutralization, 79-5764
- Virus, Bovine Leukemia**
 Viral Proteins
 Amino Acids, 79-5763
 Virus, Feline Leukemia
 Antigenic Determinants, 79-5763
- Virus, Bovine Papilloma**
 Cells, Cultured
 Cell Transformation, Neoplastic
 79-5762
 Immune Serums
 Cytopathogenic Effect, Viral, 79-5762
- Virus, C-Type RNA Tumor**
 Benz(a)anthracene, 7,12-Dimethyl-
 Binding, 79-5753
 Benzo(a)pyrene
 Binding, 79-5753
 Cholanthrene, 3-Methyl-
 Binding, 79-5753
 Lymphoma
 Virus, Helper, 79-5821
 Neoplasms, Radiation-Induced
 Sarcoma, Osteogenic, 79-5693
 Plasmacytoma
 DNA-RNA Hybridization, 79-5820
- Virus, C-Type RNA Tumor (cont'd)**
 Virus-Like Particles, 79-5820
 Rhabdomyosarcoma
 Isolation and Characterization, Snake
 79-5757
- Virus Cultivation**
 Viral Vaccines
 Carcinogenic Potential, 79-5454
 Cell Substrate, Review, 79-5454
- Virus, Cytomegalo**
 Hemangioma
 Maternal-Fetal Exchange, 79-5778
 Virus, Murine Leukemia
 Phenotypic Mixing, 79-5738
- Virus, Epstein-Barr**
 Brain Neoplasms
 Lymphoma, 79-5783
 Burkitt's Lymphoma
 Antigens, Viral, 79-5781
 DNA, Viral, 79-5780, 79-5781
 79-5782
 Nucleic Acid Hybridization, 79-5782
 Chromosomes
 Virus Activation, 79-5781
 DNA, Viral
 Cleavage Sites, 79-5780
 Endonucleases, 79-5780
 Lymphocyte Transformation, 79-5779
 Nucleotide Sequence, 79-5779
 RNA, Messenger, 79-5779
 Hodgkin's Disease
 Antibodies, Viral, 79-5764
 Infectious Mononucleosis
 DNA, Viral, 79-5780
 Lymphocyte Transformation
 Antigens, Viral, 79-5784
 Strain Difference, 79-5784
 Lymphoma
 Mouse, Nude, 79-5783
 Transplantation, Heterologous
 79-5783
 Nasopharyngeal Neoplasms
 DNA, Viral, 79-5780
 12-*O*-Tetradecanoylphorbol-13-acetate
 Co-carcinogenic Effect, 79-5626
 Uridine, 2'-Deoxy-5-iodo-
 Virus Activation, 79-5781
 Virus, Herpes Papio
 Nucleic Acid Hybridization, 79-5768
- Virus, Feline Leukemia**
 Antigens, Viral
 Histocompatibility Antigens, 79-5761
 DNA, Viral
 Nucleotide Sequence, 79-5758
 T-Lymphocytes
 Immunologic Capping, 79-5761
 Prednisolone, Methyl-
 Antigen-Antibody Reactions, 79-5759
 Lymphocyte Depletion, 79-5759
 Virus, Bovine Leukemia
 Antigenic Determinants, 79-5763
 Virus, Helper
 DNA-RNA Hybridization, 79-5758
- Virus, Feline Sarcoma**
 Antigenic Determinants
 Cell Transformation, Neoplastic
 79-5760
 DNA, Viral
 Nucleotide Sequence, 79-5758
 Lymph Nodes
 Antibodies, 79-5837
 Immunity, Cellular, 79-5837
 Sarcoma
 Graft Rejection, 79-5837
 Virus, Helper
 Viral Proteins, 79-5760
- Virus, Friend Murine Leukemia**
 Anti-Antibodies
 Immune Response, 79-5743
 Antigens
 Cell Membrane, 79-5743
 Bone Marrow
 Cell Transformation, Neoplastic

- Virus, Friend Murine Leukemia (cont'd)**
Cell Transformation, Neoplastic 79-5741
Erythroleukemia
Immune Serums, 79-5742
Genetics
Immune Response, 79-5743
Immune Response, Review, 79-5455
Glycoproteins
Antibody Specificity, 79-5742
Hematopoietic Stem Cells
Animal Model, Tupaia, 79-5741
Cell Differentiation, 79-5741
T-Lymphocytes
Suppressor Cells, Review, 79-5455
Virus, Helper
DNA-RNA Hybridization, 79-5740
- Virus, Friend Spleen Focus-Forming**
Hematopoietic Stem Cells
Carcinogenic Activity, Review 79-5456
Cell Differentiation, 79-5741
Neoplasms, Experimental
Virus, Moloney Murine Sarcoma 79-5471
RNA, Viral
Nucleotide Sequence, 79-5740
Virus, Helper, 79-5740
Viral Proteins
Immunoprecipitation, 79-5739
Virus, Moloney Murine Leukemia
DNA-RNA Hybridization, 79-5740
Virus, Rauscher Murine Leukemia
Antigenic Determinants, 79-5739
- Virus, Gibbon Ape Lymphoma**
Lymphoma
Antigenic Determinants, 79-5821
Reverse Transcriptase
Antibody Specificity, 79-5765
- Virus, Gross Murine Leukemia**
Antigens, Viral
Immunity, Cellular, 79-5744
Histocompatibility Antigens
Immunity, Cellular, 79-5744
T-Lymphocytes
Transplantation Immunology, 79-5744
- Virus, Harvey Murine Sarcoma**
Fibroblasts
Cell Transformation Neoplastic 79-5749
Phosphoproteins
Antigenic Determinants, 79-5749
- Virus, Helper**
Lymphoma
Virus, C-Type RNA Tumor, 79-5821
Virus, Radiation Leukemia, 79-5726
Virus, Abelson Murine Leukemia
Cell Transformation, Neoplastic 79-5737
Viral Proteins, 79-5760
Virus, Adeno 2
DNA, Viral, 79-5810
Virus, Feline Leukemia
DNA-RNA Hybridization, 79-5758
Virus, Feline Sarcoma
Viral Proteins, 79-5760
Virus, Friend Murine Leukemia
DNA-RNA Hybridization, 79-5740
Virus, Friend Spleen Focus-Forming
RNA, Viral, 79-5740
Virus, MC29
Replication-Defective Mutants 79-5721
Virus, Mink Cell Focus-Inducing
Viral Proteins, 79-5760
- Virus, Hepatitis**
Hepatoma
Carcinogenic Potential, 79-5490
DNA, Viral, 79-5457
Epidemiology, Review, 79-5457
Epidemiology, Tanzania, 79-5960
Liver Neoplasms
Epidemiology, 79-5943
- Virus, Hepatitis (cont'd)**
Epidemiology, Review, 79-5502
- Virus, Herpes Papio**
DNA, Circular
B-Lymphocytes, 79-5768
DNA, Viral
Nucleic Acid Hybridization, 79-5768
Virus, Epstein-Barr
Nucleic Acid Hybridization, 79-5768
- Virus, Herpes Simplex**
Genetics
Complement, 79-5769
Factor IX, 79-5769
Leukocytes
Migration Inhibitory Factor, 79-5769
- Virus, Herpes Simplex 1**
Cycloheximide
RNA, Messenger, 79-5770
DNA Polymerase
Exonuclease, 79-5771
Isolation and Characterization 79-5771
Peptides, 79-5771
DNA, Viral
RNA, Messenger, 79-5770
Virus, Adeno 5
Viral Interference, 79-5772
Virus Replication, 79-5772
- Virus, Herpes Simplex 2**
Cervix Neoplasms
Antigenic Determinants, 79-5776
Sex Behavior, Review, 79-5509
Cycloheximide
Virus Replication, 79-5774
Cytosine, 1- β -D-Arabinofuranosyl-
Virus Replication, 79-5774
DNA, Viral
Cell Transformation, Neoplastic 79-5773
Fibroblasts, Hamster, 79-5773
Fibrosarcoma
Karyotyping, 79-5775
Nucleic Acids, 79-5775
Peptides, 79-5775
Lymphosarcoma
Isolation and Characterization 79-5777
Tree Shrew, 79-5777
Ultraviolet Rays
Cell Transformation, Neoplastic 79-5773, 79-5775
Cellular Inclusions, 79-5774
Virus Replication, 79-5774
- Virus, Influenza**
Hodgkin's Disease
Antibodies, Viral, 79-5764
Thymine, 5,6-Dihydro-6-hydroperoxy-5-hydroxy-
DNA, Viral, 79-5581
Uracil, 5-Hydroperoxymethyl-
DNA, Viral, 79-5581
- Virus, Kirsten Murine Leukemia**
Reverse Transcriptase
DNA, Viral, 79-5750
- Virus, Kirsten Murine Sarcoma**
Cycloheximide
Virus Activation, 79-5747
DNA, Viral
Cell Transformation, Neoplastic 79-5745
Phenotypic Reversion, 79-5745
Fibroblasts
Cell Transformation Neoplastic 79-5749
Hematopoietic Stem Cells
Cell Differentiation, 79-5741
Imidazole-1-ethanol, 2-Methyl-5-nitro
Virus Activation, 79-5747
Peptides
Binding Sites, 79-5748
Cell Transformation, Neoplastic 79-5748
- Virus, Kirsten Murine Sarcoma (cont'd)**
Temperature Sensitive Mutants 79-5748
Phosphoproteins
Antigenic Determinants, 79-5749
Temperature Sensitive Mutants 79-5749
Reverse Transcriptase
DNA, Viral, 79-5750
Sarcoma, Osteogenic
Cycloheximide, 79-5746
Virus Activation
Protease Inhibitors, 79-5747
- Virus-Like Particles**
Plasmacytoma
IgA, 79-5820
Virus, C-Type RNA Tumor, 79-5820
Sarcoma, Osteogenic
Radium, 79-5693
Thorium, 79-5693
Sminthopsis crassicaudata
A-Type Particles, 79-5819
- Virus, Marek's Disease Herpes**
B-Lymphocytes
Antilymphocyte Serum, 79-5723
T-Lymphocytes
Antilymphocyte Serum, 79-5723
Genetic Resistance, 79-5724
Virus Replication, 79-5724
Lymphoma
DNA-RNA Hybridization, 79-5722
DNA, Viral, 79-5722
Immunization, 79-5720
Macrophages
Uridine, 2'-Deoxy-5-iodo-, 79-5723
Virus Replication, 79-5723
- Virus, Mason-Pfizer Monkey**
Rhabdomyosarcoma
Virus Replication, 79-5766
Virus Replication
Cell Cycle Kinetics, 79-5766
- Virus, MC29**
Virus, Helper
Replication-Defective Mutants 79-5721
Virus, Rous-Associated
Genetic Recombination, 79-5721
- Virus, Mink Cell Focus-Inducing**
Antigenic Determinants
Cell Transformation, Neoplastic 79-5760
Viral Proteins
Virus, Helper, 79-5760
- Virus, Moloney Murine Leukemia**
Reverse Transcriptase
DNA, Viral, 79-5750
RNA, Transfer
DNA Replication, 79-5752
Nucleotide Sequence, 79-5752
RNA, Viral
DNA Replication, 79-5752
Virus, Friend Spleen Focus-Forming
DNA-RNA Hybridization, 79-5740
- Virus, Moloney Murine Sarcoma**
Neoplasms, Experimental
Mouse, Nude, Review, 79-5471
Virus, Friend Spleen Focus-Forming 79-5471
Protein Kinase
Reverse Transcriptase, 79-5751
- Virus, Mumps**
Ovarian Neoplasms
Immune Response, 79-5954
- Virus, Murine Leukemia**
Anemia, Hemolytic
Immunization, 79-5725
Antigens, Viral
Transplantation Immunology, 79-5725
Homologous Wasting Disease
Immunization, 79-5725
Immunization

- Virus, Murine Leukemia (cont'd)**
 Lymphocytes, 79-5725
Lymphoma
 Benz(a)anthracene, 7,12-Dimethyl-
 79-5728
 Isolation and Characterization, Tissue
 Culture, 79-5728
 Neoplasm Regression, 79-5725
 Mammary Neoplasms, Experimental
 Antigens, Viral, 79-5735
 Neoplasm Regression
 Immunologic Technics, 79-5725
 Uridine, 5-Bromo-2'-deoxy-
 Virus Activation, 79-5727
 Uridine, 2'-Deoxy-5-iodo-
 Virus Activation, 79-5727
 Virus, Cytomegalo
 Phenotypic Mixing, 79-5738
- Virus, Murine Mammary Tumor**
 Antigens, Viral
 Antigenic Determinants, 79-5735
 Cell Membrane, 79-5735
 Immune Response, Review, 79-5458
 Breast Neoplasms
 Nucleic Acid Hybridization, Review
 79-5458
 Virus-Like Particles, Review, 79-5508
Genetics
 Transmission, Review, 79-5458
Glycoproteins
 Antigen-Antibody Reactions, 79-5731
 Lymphocyte Transformation, 79-5731
 Mammary Neoplasms, Experimental
 Antigen-Antibody Reactions, 79-5731
 Antigens, Viral, 79-5735
 Carbamic Acid, Ethyl Ester, 79-5734
 DNA-RNA Hybridization, 79-5733
 Horizontal Transmission, 79-5736
 Hyperplasia, 79-5732
 Immunity, Cellular, 79-5731
 Parity, 79-5736
 Prolactin, 79-5734
 Radiation, Ionizing, 79-5734
 Reverse Transcriptase
 Transmission, Review, 79-5458
RNA, Viral
 Strain Difference, 79-5733
Viral Proteins
 Isolation and Characterization
 79-5730
 Peptides, 79-5730
- Virus, Murine Sarcoma**
 Protein Kinase
 Actin, 79-5729
 Phosphoproteins, 79-5729
 Tubulin, 79-5729
 Transfection
 Transformation, Genetic, 79-5708
- Virus, Papilloma**
 Condylomata Acuminata
 Precancerous Conditions, 79-5921
 Peptides
 Immunization, 79-5785
 Warts
 Peptides, 79-5785
- Virus, Polio**
 HeLa Cells
 RNA Replicase, 79-5822
 Melanoma
 Cytopathogenic Effect, Viral, 79-5991
- Virus, Polyoma**
 DNA Replication
 RNA, Messenger, 79-5786
 DNA, Viral
 Antigens, Neoplasm, 79-5786
 Nucleotide Sequence, 79-5786
 Homologous Wasting Disease
 Interferon, 79-5787
 Interferon
 Anti-Antibodies, 79-5787
 Immune Response, Mouse, 79-5787
 Neoplasms, Experimental
 Mouse, Nude, Review, 79-5471
- Virus, Polyoma (cont'd)**
 RNA, Messenger
 Nucleic Acid Homology, 79-5788
- Virus, Polyoma, BK**
 Brain Neoplasms
 Carcinogenic Potential, Hamster
 79-5791
 Ependymoma, 79-5791
 Papilloma, 79-5791
 Cells, Cultured
 Tumorigenicity, 79-5790
 DNA, Viral
 Nucleotide Sequence, 79-5788
 Islet Cell Tumor
 Carcinogenic Potential, Hamster
 79-5791
 Karyotyping
 Cell Transformation, Neoplastic
 79-5790
 RNA, Messenger
 Cell Transformation, Neoplastic
 79-5789
 Nucleotide Sequence, 79-5789
 Sarcoma, Osteogenic
 Carcinogenic Potential, Hamster
 79-5791
- Virus, Polyoma, JC**
 DNA, Viral
 Nucleotide Sequence, 79-5788
- Virus, Radiation Leukemia**
 Leukemia
 Antigens, Viral, 79-5754
 Lymphoma
 Macrophages, 79-5829
 Replication Defective Mutants
 79-5726
 Virus, Helper, 79-5726
 Virus, Rauscher Murine Leukemia
 Antigenic Determinants, 79-5754
- Virus, Rat Sarcoma**
 Fibroblasts
 Cell Transformation Neoplastic
 79-5749
 Phosphoproteins
 Antigenic Determinants, 79-5749
- Virus, Rauscher Murine Leukemia**
 Benzo(a)pyrene
 Reverse Transcriptase, 79-5753
Brucella abortus
 Cellularity, Spleen, 79-5756
 Megakaryocytes, Plasma Cells
 79-5756
 Glycopeptides
 Isolation and Characterization
 79-5755
 Hematopoietic Stem Cells
 Carcinogenic Activity, Review
 79-5456
 Leukemia
 Antigens, Viral, 79-5754
 Reverse Transcriptase
 DNA, Viral, 79-5750
 Virus, Friend Spleen Focus-Forming
 Antigenic Determinants, 79-5739
 Virus, Radiation Leukemia
 Antigenic Determinants, 79-5754
 Virus, Sindbis
 Antigenic Determinants, 79-5755
- Virus, Recombinant**
 Virus, Rous Sarcoma
 Phenotype, 79-5715
- Virus, Reo 3**
 Radiation, Ionizing
 RNA Polymerase, 79-5687
 Virus Activation, 79-5687
- Virus Replication**
 Rhabdomyosarcoma
 Virus, Mason-Pfizer Monkey, 79-5766
 Virus, Adeno 2
 Morphological Revertants, 79-5818
 Virus, Adeno 4
- Virus Replication (cont'd)**
 Lysosomes, 79-5812
 Virus, Adeno 5
 Cell Transformation, Neoplastic
 79-5772
 Virus, Adeno 31
 Lysosomes, 79-5812
 Virus, Avian Sarcoma
 Transformation Defective Mutants
 79-5710
 Virus, Herpes Simplex 1
 Virus, Adeno 5, 79-5772
 Virus, Herpes Simplex 2
 Cycloheximide, 79-5774
 Cytosine, 1- β -D-Arabinofuranosyl-
 79-5774
 Ultraviolet Rays, 79-5774
 Virus, Marek's Disease Herpes
 T-Lymphocytes, 79-5724
 Macrophages, 79-5723
 Virus, Mason-Pfizer Monkey
 Cell Cycle Kinetics, 79-5766
 Virus, Rous Sarcoma
 Mitochondria, 79-5714
 Virus, Turkey Herpes
 T-Lymphocytes, 79-5724
- Virus, Rous-Associated**
 Antigens, Viral
 Bursa of Fabricius, 79-5718
 Chick Embryo, 79-5718
 Lymphoma
 Carcinogenic Potential, 79-5720
 Virus, MC29
 Genetic Recombination, 79-5721
- Virus, Rous Sarcoma**
 Cell Transformation, Neoplastic
 Genes, Viral, 79-5713
 Cytochrome Oxidase
 Camptothecin, 79-5714
 Chloramphenicol, 79-5714
 Ethidium Bromide, 79-5714
 DNA, Neoplasm
 Nucleotide Sequence, 79-5711
 DNA, Viral
 Cell Transformation, Neoplastic
 79-5709
 DNA-RNA Hybridization, 79-5713
 NIH/3T3 Cells, 79-5708
 Transformation, Genetic, 79-5708
 Glycoproteins
 Hexoses, 79-5706
 Lymphocyte Transformation
 Antigenic Determinants, 79-5825
 T-Lymphocytes
 Immunity, Cellular, 79-5825
 Mitochondria
 Virus Replication, 79-5714
 Procollagen
 Cell Transformation, Neoplastic
 79-5716
 RNA, Messenger, 79-5712, 79-5716
 RNA, Viral
 DNA-RNA Hybridization, 79-5717
 Isolation and Characterization
 79-5717
 Sarcoma
 DNA-RNA Hybridization, 79-5711
 Histocompatibility Antigens, 79-5702
 Ultraviolet Rays
 Deletion Mutants, 79-5713
 DNA, Viral, 79-5713
 Virus, Avian Leukosis
 Antigenic Determinants, 79-5702
 Virus, Recombinant
 Phenotype, 79-5715
- Virus, Simian Adeno 7**
 Benz(a)anthracene, 7,12-Dimethyl-
 Cell Transformation, Neoplastic
 79-5640
 Cholanthrene, 3-Methyl-
 Cell Transformation, Neoplastic
 79-5640
 Methanesulfonic Acid, Methyl Ester
 DNA, Viral, 79-5640
 Sulfuric Acid, Nickel Salt

Virus, Simian Adeno 7 (cont'd)
DNA, Viral, 79-5640

Virus, Simian Adeno 38
DNA Restriction Enzyme
Cleavage Sites, 79-5767
DNA, Viral
Physicochemical Properties, 79-5767

Virus, Simian Sarcoma
Hodgkin's Disease
Antibodies, Viral, 79-5764
Lymphoma
Antigenic Determinants, 79-5821
Reverse Transcriptase
Antibody Specificity, 79-5765

Virus, Sindbis
Virus, Rauscher Murine Leukemia
Antigenic Determinants, 79-5755

Virus, SV40
Adenosine, *N*-Methyl-
RNA, Messenger, 79-5796
RNA, Viral, 79-5796
Antigens, Neoplasm
Phosphoproteins, 79-5801
Protein Kinase, 79-5801
Antigens, Viral
Intracellular Distribution, 79-5807
Temperature Sensitive Mutants
79-5807
Bacteriophages
Nucleic Acid Hybridization, 79-5799
Transformation, Genetic, 79-5799
Concanavalin A
Antigens, Neoplasm, 79-5804
Immunization, 79-5804
T-Lymphocytes, 79-5804
DNA, Single Stranded
Cell Transformation, Neoplastic
79-5798
DNA-RNA Hybridization, 79-5798
DNA, Viral
Antigens, Neoplasm, 79-5792
Chromatin, 79-5794
Deletion Mutants, 79-5793
Depurination, 79-5797
Methanesulfonic Acid, Methyl Ester
79-5797
Nuclear Morphology, 79-5792
Nucleotide Sequence, 79-5788
RNA, Messenger, 79-5793
RNA Polymerase, 79-5794, 79-5795
Temperature Sensitive Mutants
79-5800

Virus, SV40 (cont'd)
Transformation, Genetic, 79-5799
79-5800
Histocompatibility Antigens
Immunity, Cellular, 79-5803
T-Lymphocytes, 79-5803
Histones
Chromatin, 79-5802
Lysosomes
Acid Phosphatase, 79-5805
Cytopathogenic Effect, Viral, 79-5805
Meningioma
Antigens, Neoplasm, 79-5806
RNA, Messenger
Adenosine Triphosphate, 79-5795
Nucleotide Sequence, 79-5789
79-5795
Sarcoma
Histocompatibility Antigens, 79-5836
Transplantation Immunology, 79-5836
Viral Proteins
Chromatin, 79-5802
Nuclear Morphology, 79-5792
Xeroderma Pigmentosum
DNA Repair, 79-5797

Virus, Turkey Herpes
T-Lymphocytes
Virus Replication, 79-5724

Warts
Virus, Papilloma
Peptides, 79-5785

Water, Heavy
DNA Replication
Bone Marrow, Lymphoid Tissue
79-5676
Lung Neoplasms
Carcinogenic Activity, Rat, 79-5676
Soft Tissue Neoplasms
Carcinogenic Activity, Rat, 79-5676

Water Pollutants
Benzo(a)pyrene
Chromosome Aberrations, 79-5645
Chromosome Aberrations
Lymphocyte Culture Technique
79-5645
Polymers
Quantitation Method, Review, 79-5430

Wood
Paranasal Sinus Neoplasms
Occupational Hazard, 79-5601

Wounds and Injuries
Bladder Neoplasms
Cytoscopy, Review, 79-5486
Sarcoma
Case Report, 79-5885
Neoplasm Recurrence, Local, 79-5885

Xanthine, 3-Hydroxy-
Hepatoma
Structure-Activity Relationship
79-5594
Sarcoma
Structure-Activity Relationship
79-5594

Xanthine Oxidase
Cell Transformation, Neoplastic
Enzymatic Activity, 79-5978
Contact Inhibition
Enzymatic Activity, 79-5978
Hepatoma
Virus, Avian Leukosis, 79-5703

Xenopus laevis
Interferon
Oocytes, 79-5976
Milk Proteins
Oocytes, 79-5976
RNA, Messenger
Interferon, 79-5976
Milk Proteins, 79-5976

Xeroderma Pigmentosum
Pyrimidine Nucleotides
Fibroblasts, 79-5993
Ultraviolet Rays
Chromatids, 79-5680
DNA Repair, Review, 79-5448
Urea, Ethyl Nitroso-
DNA, Alkylation, 79-5993
Virus, SV40
DNA Repair, 79-5797

Yttrium Radioisotopes
Carcinoma, Epidermoid
Inhalation Study, Dog, 79-5684
Nose Neoplasms
Carcinoma, Epidermoid, 79-5684
Sarcoma, Osteogenic
Strontium, 79-5678

У. 67.1. УИЗБАНА - СИЛЛАРА

Chemical Abstracts Service Registry Number Index

- 35-25-6, 79-05483
50-00-0, 79-05445
50-02-2, 79-05662, 79-05700, 79-05704
50-04-4, 79-05833
50-06-6, 79-05402, 79-05532, 79-05602
79-05609, 79-05616, 79-05618
79-05638
50-07-7, 79-05540, 79-05577, 79-05675
79-05830
50-18-0, 79-05573, 79-05574, 79-05575
79-05577, 79-05930
50-21-5, 79-05706, 79-05977
50-22-6, 79-05670
50-27-1, 79-05438, 79-05508
50-28-2, 79-05438, 79-05637, 79-05670
50-29-3, 79-05402, 79-05526
50-32-8, 79-05433, 79-05445, 79-05609
79-05621, 79-05629, 79-05645
79-05646, 79-05647, 79-05648
79-05650, 79-05651, 79-05654
79-05655, 79-05657, 79-05658
79-05753
50-41-9, 79-05438
50-44-2, 79-05574
50-50-0, 79-05669
50-55-5, 79-05435
50-81-7, 79-05546
51-03-6, 79-05553
51-18-3, 79-05583
51-71-8, 79-05548
51-75-2, 79-05586
51-79-6, 79-05734
52-24-4, 79-05530, 79-05539, 79-05574
79-05575
53-06-5, 79-05462
53-16-7, 79-05997
53-70-3, 79-05433
53-85-0, 79-05811
53-94-1, 79-05551
53-95-2, 79-05551, 79-05553
53-96-3, 79-05489, 79-05551, 79-05552
79-05553, 79-05628, 79-05629
54-42-2, 79-05723, 79-05727, 79-05781
55-18-5, 79-05412, 79-05489, 79-05560
79-05561, 79-05562, 79-05563
55-91-4, 79-05979
55-98-1, 79-05573, 79-05574, 79-05577
56-12-2, 79-05980
56-23-5, 79-05433
56-49-5, 79-05532, 79-05552, 79-05609
79-05621, 79-05638, 79-05639
79-05640, 79-05641, 79-05642
79-05644, 79-05646, 79-05653
79-05753, 79-05835
56-53-1, 79-05437, 79-05438, 79-05637
79-05667, 79-05668, 79-05670
79-05671
56-55-3, 79-05657
56-57-5, 79-05592
56-65-5, 79-05795, 79-05977
56-75-7, 79-05589, 79-05714
57-22-7, 79-05930
57-63-6, 79-05503, 79-05941
57-83-0, 79-05997
57-88-5, 79-05505, 79-05988
57-97-6, 79-05553, 79-05627, 79-05628
79-05629, 79-05630, 79-05631
79-05632, 79-05633, 79-05635
79-05636, 79-05637, 79-05640
79-05657, 79-05685, 79-05728
79-05753
58-08-2, 79-05688
58-15-1, 79-05546
58-22-0, 79-05666
58-55-9, 79-05595, 79-05596
58-61-7, 79-05554
58-89-9, 79-05417
59-05-2, 79-05512, 79-05540, 79-05590
59-14-3, 79-05727
59-89-2, 79-05489, 79-05593
59-92-7, 79-05632
60-34-4, 79-05549
60-51-5, 79-05530
60-92-4, 79-05563, 79-05625
62-44-2, 79-05612
62-57-7, 79-05623
62-75-9, 79-05412, 79-05413, 79-05517
79-05546, 79-05559, 79-05565
79-05575
64-17-5, 79-05502, 79-05518, 79-05578
79-05888, 79-05889, 79-05959
79-05965
65-46-3, 79-05554
65-47-4, 79-05466
65-71-4, 79-05581
66-27-3, 79-05576, 79-05577, 79-05586
79-05628, 79-05640, 79-05797
66-75-1, 79-05590
66-81-9, 79-05544, 79-05746, 79-05747
79-05770, 79-05774
67-68-5, 79-05984
67-73-2, 79-05633
68-12-2, 79-05999
68-26-8, 79-05965
70-18-8, 79-05592, 79-05618
70-25-7, 79-05559, 79-05576, 79-05577
79-05579, 79-05589, 79-05746
70-26-8, 79-05980
71-43-2, 79-05418, 79-05605, 79-05932
71-55-6, 79-05523
72-20-8, 79-05434
72-33-3, 79-05503, 79-05941
72-55-9, 79-05529
74-85-1, 79-05445
75-01-4, 79-05403, 79-05436, 79-05437
79-05527, 79-05528, 79-05575
75-09-2, 79-05523
78-93-3, 79-05654
79-01-6, 79-05401, 79-05523, 79-05528
79-81-2, 79-05535
81-07-2, 79-05613
83-43-2, 79-05759
85-30-3, 79-05554
88-05-1, 79-05407
91-59-8, 79-05403, 79-05617
94-75-7, 79-05413
96-09-3, 79-05598, 79-05602, 79-05604
79-05608
97-00-7, 79-05849
97-77-8, 79-05558
99-54-7, 79-05604
100-02-7, 79-05551
100-41-4, 79-05609
100-42-5, 79-05608, 79-05609
104-87-0, 79-05607
106-93-4, 79-05521, 79-05522
108-88-3, 79-05418, 79-05523, 79-05605
79-05654
108-95-2, 79-05557
110-91-8, 79-05593
115-32-2, 79-05526
121-79-9, 79-05603
123-33-1, 79-05610
126-72-7, 79-05531
126-85-2, 79-05574
127-18-4, 79-05523
128-37-0, 79-05599, 79-05600
141-05-9, 79-05608
147-84-2, 79-05578
147-94-4, 79-05540, 79-05774
150-76-5, 79-05603
151-18-8, 79-05636
151-56-4, 79-05530
151-67-7, 79-05524, 79-05525
153-78-6, 79-05551
154-17-6, 79-05977
244-63-3, 79-05582, 79-05655
288-13-1, 79-05578
298-81-7, 79-05447
302-01-2, 79-05590

- 302-79-4, 79-05644
303-45-7, 79-05674
305-03-3, 79-05540
305-84-0, 79-05980
362-74-3, 79-05632
366-70-1, 79-05930
398-32-3, 79-05407
421-20-5, 79-05545
443-48-1, 79-05585, 79-05586, 79-05587
79-05747
446-86-6, 79-05863
486-84-0, 79-05582, 79-05655
506-32-1, 79-05624
506-68-3, 79-05990
519-23-3, 79-05646
540-73-8, 79-05547, 79-05843
551-93-9, 79-05673
568-70-7, 79-05631
568-75-2, 79-05631
578-76-7, 79-05567, 79-05584
590-96-5, 79-05515
592-62-1, 79-05516, 79-05517
604-59-1, 79-05646, 79-05649
613-13-8, 79-05647
615-05-4, 79-05551
616-07-9, 79-05980
616-91-1, 79-05580
621-64-7, 79-05413
642-65-9, 79-05407
671-16-9, 79-05577, 79-05606, 79-05930
684-93-5, 79-05565, 79-05566, 79-05567
79-05575, 79-05579
738-99-8, 79-05530
758-17-8, 79-05549
759-73-9, 79-05568, 79-05569, 79-05570
79-05891, 79-05993
865-21-4, 79-05930
892-17-1, 79-05597
915-67-3, 79-05402
930-55-2, 79-05412, 79-05414, 79-05578
937-14-4, 79-05620
961-11-5, 79-05538
964-21-6, 79-05588
1083-48-3, 79-05526
1116-54-7, 79-05413
1162-65-8, 79-05407, 79-05490, 79-05618
79-05619, 79-05620, 79-05621
79-05646
1239-45-8, 79-05646, 79-05714
1305-78-8, 79-05535
1314-20-1, 79-05436
1332-21-4, 79-05403, 79-05404, 79-05433
79-05533, 79-05974
1333-82-0, 79-05536
1385-95-1, 79-05620
- 1407-15-4, 79-05574
1746-01-6, 79-05433, 79-05519, 79-05520
1845-11-0, 79-05438
1867-73-8, 79-05796
2122-77-2, 79-05519, 79-05520
2318-18-5, 79-05572
2438-80-4, 79-06000
2485-10-1, 79-05407
2564-65-0, 79-05631
2642-81-1, 79-05526
2642-98-0, 79-05552
3067-13-8, 79-05656, 79-05660
3067-14-9, 79-05656, 79-05660
3083-23-6, 79-05608
3308-64-3, 79-05642
3416-24-8, 79-06000
3483-12-3, 79-05688
3688-53-7, 79-05585
3817-11-6, 79-05558, 79-05643
3902-71-4, 79-05692
4075-79-0, 79-05553
4463-22-3, 79-05553
4759-48-2, 79-05643
4891-15-0, 79-05574
5142-23-4, 79-05567
6051-87-2, 79-05551
6098-44-8, 79-05617
6136-37-4, 79-05596
6276-06-8, 79-05556
6292-55-3, 79-05556
6898-94-8, 79-05980
7429-90-5, 79-05939
7439-88-5, 79-05683
7439-89-6, 79-05892, 79-05973
7439-92-1, 79-05453, 79-05499
7439-96-5, 79-05986
7439-97-6, 79-05434
7440-08-6, 79-05453, 79-05697
7440-38-2, 79-05498, 79-05534
7440-41-7, 79-05533
7440-43-9, 79-05935
7440-61-1, 79-05690, 79-05694
7631-90-5, 79-05543
7632-00-0, 79-05557, 79-05593
7689-03-4, 79-05714
7697-37-2, 79-05926
7723-14-0, 79-05985
7727-37-9, 79-05568
7771-44-0, 79-05624
7778-50-9, 79-05536, 79-05537
7782-44-7, 79-05568
7782-49-2, 79-05405
- 7782-77-6, 79-05410
7786-81-4, 79-05640
8001-28-3, 79-05654
8002-05-9, 79-05832
8008-20-6, 79-05650
9001-45-0, 79-05651, 79-05844
9001-78-9, 79-05844
9002-62-4, 79-05595, 79-05663, 79-05734
79-05997
9002-72-6, 79-05595
9004-10-8, 79-05483
9008-11-1, 79-05187, 79-05976
9014-02-2, 79-05574
9035-50-1, 79-05518, 79-05600, 79-05602
79-05607, 79-05638, 79-05647
79-05657
10043-92-2, 79-05453, 79-05679
10045-97-3, 79-05684, 79-05927
10098-91-6, 79-05678, 79-05684
10102-44-0, 79-05546
10588-01-9, 79-05537
11028-71-0, 79-05670, 79-05804, 79-06000
11056-06-7, 79-05540
12001-28-4, 79-05403, 79-05404, 79-05433
79-05533, 79-05974
12001-29-5, 79-05403, 79-05404, 79-05433
79-05533, 79-05974
12035-72-2, 79-05536
12172-73-5, 79-05403, 79-05404, 79-05433
79-05533, 79-05974
13010-07-6, 79-05590, 79-05591
13233-32-4, 79-05678, 79-05693
13345-21-6, 79-05649, 79-05653, 79-05660
13345-23-8, 79-05649
13479-29-3, 79-05594
13967-73-2, 79-05678, 79-05684, 79-05927
13981-16-3, 79-05450, 79-05452, 79-05682
79-05686
14901-08-7, 79-05490
15183-39-8, 79-05413
15623-47-9, 79-05693
15663-27-1, 79-05541, 79-05542
15687-27-1, 79-05884
16033-21-9, 79-05584
16543-55-8, 79-05414
16561-29-8, 79-05622, 79-05623, 79-05624
79-05625, 79-05626, 79-05633
79-05815
16812-54-7, 79-05536
16941-32-5, 79-05483
16984-48-8, 79-05682
17068-78-9, 79-05403, 79-05404, 79-05433
79-05533, 79-05974
17573-29-4, 79-05649, 79-05653, 79-05660
20449-79-0, 79-05624
20535-83-5, 79-05567, 79-05579, 79-05584
79-05589

20535-83-5 (cont'd)	35693-99-3, 79-05616	57303-99-8, 79-05651, 79-05655, 79-05658 79-05660
20830-81-3, 79-05574	37132-72-2, 79-05530	59960-30-4, 79-05571
22225-32-7, 79-05556	37574-47-3, 79-05652	59963-01-8, 79-05659, 79-05661
23214-92-8, 79-05573, 79-05574, 79-05590	39386-07-7, 79-05469, 79-05729	61811-29-8, 79-05628
24554-26-5, 79-05539, 79-05540	47830-26-2, 79-05595, 79-05997	64091-91-4, 79-05414
24909-09-9, 79-05651	50607-67-5, 79-05796	64551-89-9, 79-05634
25013-16-5, 79-05516, 79-05599, 79-05603 79-05604	51131-85-2, 79-05646	69112-99-8, 79-05571
25614-03-3, 79-05595, 79-05997	51481-61-9, 79-05415, 79-05416	69113-00-4, 79-05571
26409-15-4, 79-05595, 79-05997	51810-90-3, 79-05611	69113-01-5, 79-05571
26594-44-5, 79-05554, 79-05555	53609-64-6, 79-05564	69467-92-1, 79-05646
26628-22-8, 79-05406	54350-48-0, 79-05633	
27208-37-3, 79-05650	56484-47-0, 79-05651	
	56856-83-8, 79-05550	

У. 67.1. ОБЩАЯ - СИМПАТОМ

Wiswesser Line Notation Index

.AL, 79-5939
 .AS, 79-5498, 79-5534
 .BE, 79-5533
 .CA..O, 79-5535
 .CD 79-5935
 .CR..O3, 79-5536
 .CS, 79-5684, 79-5927
 .FE, 79-5892, 79-5973
 .HG, 79-5434
 .IR, 79-5683
 .KA2. CR2-O5-Q2, 79-5536, 79-5537
 .MN, 79-5986
 .N, 79-5568
 .NA..N-O-Q, 79-5557, 79-5593
 .NA..S-O3, 79-5543
 .NA2. CR2-O5-Q2, 79-5537
 .NI..S-O4, 79-5640
 .NI3.S2, 79-5536
 .P, 79-5985
 .PB, 79-5453, 79-5499
 .PO, 79-5453, 79-5697
 .PU 79-5450, 79-5452, 79-5682, 79-5686
 .RA 79-5678, 79-5693
 .RN, 79-5453, 79-5679
 .SE, 79-5405
 .SR, 79-5678, 79-5684, 79-5927
 .TH, 79-5693
 .TH..O2, 79-5436
 .UR, 79-5690, 79-5694
 .Y, 79-5678, 79-5684
 E CN, 79-5990
 E1YE1O 3PO, 79-5531
 E2E, 79-5521, 79-5522
 FR DR, 79-5407
 GR D- 2BT3OTJ, 79-5526
 GR DYU1&R DG, 79-5526
 GXGGG, 79-5433
 GXGGXQR DG&R DG, 79-5526
 GXGGYR DG&R DG, 79-5402, 79-5526
 GXGG1, 79-5523
 GYEXFFF, 79-5524, 79-5525
 GYGUYGG, 79-5523
 GYGUYR DG&R DG, 79-5529
 GYGU1G, 79-5401, 79-5523, 79-5528
 G1G, 79-5523
 G1UR BG DG EG&OPO&O1&O1&O1
 79-5538
 G1U1, 79-5403, 79-5436, 79-5437, 79-5527
 79-5528, 79-5575
 G2KO&2G, 79-5574

G2N1&2G, 79-5586
 IVMR DR, 79-5553
 L B656 HHJ DMV1, 79-5556
 L B656 HHJ DMV1 HQ, 79-5586
 L B656 HHJ EMQ, 79-5551
 L B656 HHJ EMV1, 79-5489, 79-5551
 79-5552, 79-5553, 79-5628, 79-5629
 L B656 HHJ ENOV1&V1, 79-5617
 L B656 HHJ ENQV1, 79-5551, 79-5553
 L B656 HHJ ENV1&V1, 79-5407
 L B666J HHJ EZ, 79-5551
 L C666J EZ, 79-5647
 L D6 B666 QUS&&&TJ OQ PQ, 79-5634
 L D6 B666J, 79-5657
 L D6 B666J C1 J1, 79-5553, 79-5627
 79-5628, 79-5629, 79-5630, 79-5631
 79-5632, 79-5633, 79-5635, 79-5636
 79-5637, 79-5640, 79-5657, 79-5685
 79-5728, 79-5753
 L D6 B666J C1 J1Q, 79-5631
 L D6 B666J C1Q J1, 79-5631
 L D6 B666J C1Q J1Q, 79-5631
 L D6 B6666 2AB TJ, 79-5433, 79-5445
 79-5609, 79-5621, 79-5629, 79-5645
 79-5646, 79-5647, 79-5648, 79-5650
 79-5651, 79-5654, 79-5655, 79-5657
 79-5658, 79-5753
 L D6 B6666 2AB TJ EQ FQ, 79-5651
 L D6 B6666 2AB TJ FQ, 79-5649
 79-5653, 79-5660
 L D6 B6666 2AB TJ GQ HQ, 79-5651
 79-5655, 79-5658, 79-5660
 L D6 B6666 2AB TJ OQ, 79-5649
 79-5653, 79-5660
 L E5 B666 FVTTT&J E1 OQ, 79-5997
 L E5 B666 GV OV MUTJ A1 CQ E1
 FV1Q -B&ACEF, 79-5462
 L E5 B666 LUTJ A1 E1 FY&3Y QQ -
 B&AEFO, 79-5505, 79-5988
 L E5 B666 OV AHTTT&J A1 CQ E1
 FV1Q FQ G1 -A&B-B&ACEFG
 79-5662, 79-5700, 79-5704
 L E5 B666 OV MU PUTJ A1 CQ E1
 FV1Q FQ L1 -B&ACEF
 79-5759
 L E5 B666 OV MUTJ A1 E1 FQ -B&AEF
 79-5666
 L E5 B666 OV MUTJ A1 E1 FV1 -
 B&AEF, 79-5997
 L E5 B666TTT&J E1 FQ F1UU1 OQ
 79-5503, 79-5941
 L E5 B666TTT&J E1 FQ GQ OQ
 79-5438, 79-5508
 L E5 B666TTT&J E1 FQ OQVR, 79-5669
 L E5 B666TTT&J E1 FQ OQ, 79-5438
 79-5637, 79-5670

L E5 D6656 1A T&&&T&J R1, 79-5532
 79-5552, 79-5609, 79-5621, 79-5638
 79-5639, 79-5640, 79-5641, 79-5642
 79-5644, 79-5646, 79-5653, 79-5753
 79-5835
 L E6 B666J MZ, 79-5552
 L E6 D6656 1A T&&&T&J OQ PQ R1
 79-5642
 L E6 D6656 1A T&&&T&J PQ R1
 79-5642
 L G6 D6 B666J, 79-5433
 L6TJ AG BG CG DG EG FG *GAMMA
 79-5417
 L6UTJ A1 A1 B1U1Y1&UZU1YU1VQ&1
 C1 -T, 79-5644
 L6UTJ A1 BL/U1Y1&U2/ 2Q C1 C1 -T
 79-5965
 L66J BSWQ ENUN- BL66J CQ DSWQ
 HSWQ &-NA- 3, 79-5402
 L66J CZ, 79-5403, 79-5617
 ONN1&VN2G&2G, 79-5571
 ONN1&1, 79-5412, 79-5413, 79-5517
 79-5546, 79-5559, 79-5565, 79-5575
 ONN1&1OV1, 79-5550
 ONN1V1&1V1, 79-5564
 ONN1YQ1&1YQ1, 79-5564
 ONN2&2, 79-5412, 79-5489, 79-5560
 79-5561, 79-5562, 79-5563
 ONN2G&VN1&1, 79-5571
 ONN2G&VN2&2, 79-5571
 ONN2G&VN2G&2G, 79-5571
 ONN2Q&2Q, 79-5413
 ONN3&3, 79-5413
 ONO, 79-5546
 ON1&UN1OV1, 79-5516, 79-5517
 OO, 79-5568
 OS1&1, 79-5984
 QR, 79-5557
 QR BQ CQ EVO3, 79-5603
 QR DO1, 79-5603
 QR DY2& 2U, 79-5437, 79-5438, 79-5637
 79-5667, 79-5668, 79-5670, 79-5671
 QVYZ1R CQ DQ -L, 79-5632
 QV3R DN2G2G, 79-5540
 QV4U3U3U3U6, 79-5624
 QYVQ, 79-5706, 79-5977
 Q1NUNO&1, 79-5515
 Q1VOR BG DG, 79-5413
 Q2, 79-5502, 79-5518, 79-5578, 79-5888
 79-5889, 79-5959, 79-5965
 Q2OR BG DG EG, 79-5519, 79-5520
 Q4N4&NO, 79-5558, 79-5643
 R, 79-5418, 79-5605, 79-5932
 SH1YVQMV1 -L, 79-5580
 SUYSHN2&2, 79-5578

SIYQYQIS, 79-5688
T B656 EN HMJ FT B656 EN HMJ F1
 79-5582, 79-5655
T B666 HKJ EZ H2 IR& LZ &E &9/26
 79-5646, 79-5714
T C566 DO LVOJ BO1, 79-5447
T C566 DO LVOJ B1 E1 J1, 79-5692
T C6 B5665 2AB S BX IN QN NU
JH&&TTTJ FO1 IVH KVO1 KQ LOV1
M2E-NT F6 E596 A BN LM&&TTJ
NVO1RQ R2, 79-5930
T C6 B5665 2AB S BX IN QN NU
JH&&TTTJ FO1 I KVO1 KQ LOV1 M2
E-NT F6 E596 A BN LM&&TTJ NVO1 Q
Q2, 79-5930
T D3 B556 BN EM JV MVTTT&J GO1
H1OVZ KZ L1, 79-5540, 79-5577
 79-5675, 79-5830
T D36 I666 B6 2AB U EOT&&&&J
 79-5652
T D36 J6 H66 EOST&&&&J BQ CQ
 79-5634
T D6 B6666 2AB JV QV T&T&T&J
 79-5656, 79-5660
T E3 D5 C555 A D- FO KUTJ AG AG BG
JG KG LG, 79-5434
T E3 D6 B6666 2AB U FOTT&&&&J HQ
IQ, 79-5659, 79-5661
T F5 C6 B655 DOV GV OO QO
RUT&&TTJ LO1, 79-5407, 79-5490
 79-5618, 79-5619, 79-5620, 79-5621
 79-5646
T F6 D5 C666 EM ON&&TTTJ HO1
SOVR CO1 DO1 EO1& TO1 UVO1
 79-5435
T3MTJ, 79-5530
T3NTJ A- 3PST3NTJ A- 3PS, 79-5530
 79-5539, 79-5574, 79-5575
T3OTJ BR, 79-5598, 79-5602, 79-5604
 79-5608
T3OTJ BXGGG, 79-5608
T5MNJ, 79-5578
T5N CNJ A2Q B1 ENW, 79-5585
 79-5586, 79-5587, 79-5747
T5NNVJ A1 BR& DN1&1 E1, 79-5546
T5NTJ ANO, 79-5412, 79-5414, 79-5578
T5OJ BNW E- ET5N CSJ BMVH
 79-5539, 79-5540
T5OJ BYVZU1- BT 5OJ ENW, 79-5585
T5OTJ B1OVM2, 79-5618
T5OV EHJ CQ DQ EYQ1Q, 79-5546
T56 BM DN FMVNVJ H1, 79-5596
T56 BM DN FN HNJ ISH, 79-5574
T56 BM DN FNVNJ FQ, 79-5594
T56 BM DN FNVNVJ F1 H1, 79-5595
 79-5596

T56 BN DN FMYMVJ B1 GUM, 79-5567
 79-5584
T56 BN DN FMYMVJ GUM D- BT5OTJ
CQ DQ E1Q, 79-5554
T56 BN DN FN HNJ IM1 D- BT5OTJ
CQ DQ E1Q -A&CD
 79-5796
T56 BN DN FN HNJ IZ D- BT5OTJ CQ
DQ E1Q -A&CD, 79-5554
T56 BN DN FNVNVJ B1 F1 H1, 79-5688
T56 BO DO CHJ G3 H1O2O2O4
 79-5553
T56 BSVVMVJ, 79-5613
T6M DOTJ, 79-5593
T6MPOTJ BO BN2G2G, 79-5573
 79-5574, 79-5575, 79-5577, 79-5930
T6MVMVJ EN2G2G, 79-5590
T6MVMVJ EQ FQ, 79-5581
T6MVMVJ E1, 79-5581
T6N CN ENJ B- D- F-/- AT3NTJ 3
 79-5583
T6N DOTJ ANO, 79-5489, 79-5593
T6NJ C- BT5NTJ ANO, 79-5414
T6NTJ CV3N1&NO, 79-5414
T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C
 79-5727
T6NVMVJ E1 A- ET5OTJ B1Q CQ -A&C
 79-5723, 79-5727, 79-5781
T6NVNJ DZ A- BT5OTJ CQ DQ E1Q
 79-5540, 79-5774
T6NVNJ DZ A- ET5OTJ B1Q CQ DQ
 79-5554
T6OTJ BO1NUNO&1 CQ DQ EQ F1Q-
A&D -D, 79-5490
T6VMMVJ, 79-5610
T6VMMVJ FHJ F2 FR, 79-5402, 79-5532
 79-5602, 79-5609, 79-5616, 79-5618
 79-5638
T6VMTJ E1YQ- BL6VTJ D1 F1
 79-5544, 79-5746, 79-5747, 79-5770
 79-5774
T66 BMDN FN HNJ IS- ET5N ONJ
DNW, 79-5863
T66 BN DN GN JNJ CZ EZ H1N1&R
DVMYVQ2VQ *L DX
 79-5512, 79-5540, 79-5590
T66 BNJ BO ENW, 79-5592
T666 BO IO T&&J EG FG LG MG
 79-5433, 79-5519, 79-5520
VHH, 79-5445
VHN1&1, 79-5999
VH1R, 79-5607
VH1YQYQYQ1Q -BAA -D, 79-5977
WNMYUM&N1&NO, 79-5559, 79-5576
 79-5577, 79-5579, 79-5589, 79-5746

WNMYUM&N3&NO, 79-5590, 79-5591
WNR BG ENW, 79-5849
WNR CG DG, 79-5604
WNR DQ, 79-5551
WNR DYQY1QMUYGG -DL, 79-5589
 79-5714
WS1&O1, 79-5576, 79-5577, 79-5586
 79-5628, 79-5640, 79-5797
WS1&O2 2U -C, 79-5573, 79-5574, 79-5577
ZMR D1Q, 79-5549
ZM1, 79-5549
ZM2R, 79-5548
ZR BV1, 79-5673
ZR B1 D1 F1, 79-5407
ZR CZ DO1, 79-5551
ZVN1&NO, 79-5565, 79-5566, 79-5567
 79-5575, 79-5579
ZVN2&NO, 79-5568, 79-5569, 79-5570
 79-5891, 79-5993
ZVO2, 79-5734
ZXUQ, 79-5623
ZZ, 79-5590
Z2CN, 79-5636
Z3VQ, 79-5980
1MM1, 79-5547, 79-5843
1MNVNR, 79-5584
IOPS&O1&S1VM1, 79-5530
1R, 79-5418, 79-5523, 79-5605, 79-5654
1U1, 79-5445
1U1R, 79-5608, 79-5609
1VNQR DR, 79-5553
1VONV1&R DIV1R -T, 79-5554, 79-5555
1X1&1&R BQ CX1&1&1 E1, 79-5599
 79-5600
1Y&MVR D1MM1, 79-5577, 79-5606
1Y&MVR D1MM1 &GH, 79-5930
1Y&OPO&FOY1&1, 79-5979
1Y1&1R BQ EO1, 79-5516, 79-5599
 79-5603, 79-5604
1Y1&1R CQ FO1, 79-5516, 79-5599
 79-5603, 79-5604
2N2&YUS&S 2, 79-5558
2OR DMV1, 79-5612
2OV1U1VO2, 79-5608
2R, 79-5609
2V1 79-5654

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CARCINOGENESIS ABSTRACTS

VOLUME 17,
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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS

VOLUME 17, ISSUE 11

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page Nos.
REVIEW	(Rev)	79-6001—79-6127	2333
CHEMICAL CARCINOGENESIS	(Chem)	79-6128—79-6352	2359
PHYSICAL CARCINOGENESIS	(Phys)	79-6353—79-6378	2409
VIRAL CARCINOGENESIS	(Viral)	79-6379—79-6464	2415
IMMUNOLOGY	(Immun)	79-6465—79-6518	2434
PATHOGENESIS	(Path)	79-6519—79-6553	2446
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	79-6554—79-6589	2453
MISCELLANEOUS	(Misc)	79-6590—79-6600	2460
AUTHOR INDEX			2463
SUBJECT INDEX			2469
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2513
WISWESSER LINE NOTATION INDEX			2517

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intra-peritoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		

REVIEW

- 79-6001 Molecular-Biological Aspects of Neoplastic Transformation. (Rus) Shapot, V. S. (Moscow, USSR). *Vestn Akad Med Nauk SSSR* (Groton, CT)(8): 48-55; 1979.

A critical review of current data on the molecular mechanisms of neoplastic transformation is presented. The recent discovery of stable binding of DNA with protein in the chromatin of Zajdela ascites hepatoma cells contradicts the widely accepted hypothesis that derepression of the genome is a universal feature of the cancer cell. It is emphasized that the regulation of nuclear-cytoplasmic transfer of messenger RNA plays an extremely important role in the realization of the oncogenic potential of the cell genome. (64 refs)

- 79-6002 Toxaphene, a Complex Mixture of Polychloroterpenes and a Major Insecticide, Is Mutagenic. (Eng) Hooper, N. K. (Dept. Biochemistry, Univ. California, Berkeley, CA 94720); Ames, B. N.; Saleh, M. A.; Casida, J. E. *Science* 205(4406): 591-593; 1979.

Toxaphene, the most widely used chlorinated insecticide, was mutagenic to *Salmonella typhimurium* strains TA98 and TA100 in the absence of a liver homogenate. This insecticide is a complex mixture (>177 polychloroterpenes) with carcinogenic activity in rodents. Some, but not all, of the mutagenic components were easily separated from the insecticidal ingredients. (26 refs)

- 79-6003 Carcinogenicity of Toxaphene: A Review. (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD 21701). *J Toxicol Environ Health* 5(4): 729-748; 1979.

All known studies of the carcinogenicity of toxaphene (TP) are reviewed. TP is highly carcinogenic in rats and mice. It induced malignant neoplasms of the liver in rats. In addition, benign and malignant neoplasms at all sites were increased in male and female rats ingesting TP. Sarcomas were found more often in male rats, carcinomas in female rats. Neoplasms of the endocrine organs were also increased in male and female TP-treated rats. The incidence of neoplasms of the reproductive system was increased in female rats, as was the incidence of mammary gland neoplasms in male rats. Toxic changes in male rats given TP included interstitial fibrosis of the kidney and atrophy of the testes. TP induced malignant neoplasms of the liver in male and female mice. The incidence of malignant neoplasms at all sites was also increased. In addition to hepatic neoplasms, male mice had leukemia or lymphosarcoma, and females had sarcomas of the uterus. (23 refs)

- 79-6004 Are Benzene Effects Limited to the Chromosomal Level? (Eng) Ray, V. (Medical Res. Lab., Pfizer, Inc.). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Of-*

fice of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978. McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 201-206; 1979.

The possibility that the mutagenic effects of benzene are limited to the chromosomal level is reviewed. In tests with and without metabolic activation, benzene did not produce point mutations. At the chromosomal levels, both in vitro and in vivo, benzene was shown to cause chromatid-type breaks, dicentric and ring forms, chromatid deletions, and chromosomal breaks. Of two human studies, one showed no cytogenic effects in 290 persons exposed to benzene over a 10-yr period; the other showed a significant cytogenic effect in 52 exposed individuals, this effect involving chromosome breaks and marker chromosomes. Data obtained in dominant lethal experiments have been negative. (26 refs)

- 79-6005 The Carcinogenic and Other Chronic Effects of Persistent Halogenated Organic Compounds. (Eng) Kimbrough, R. D. (Toxicology Branch, Center Disease Control, Dept. Health, Education and Welfare, Atlanta, GA 30333). *Ann NY Acad Sci* 320: 415-418; 1979.

The chronic effects of persistent halogenated organic compounds are reviewed. These compounds induce mixed function oxidases and cause hepatomegaly in rodents and other mammals. The halogenated dibenzo-dioxins and hexachlorobenzene induce experimental hepatic porphyria, and the polychlorinated biphenyls (PCBs) and technical pentachlorophenyl cause adenofibrosis in rats. Adenofibrosis usually occurs concomitantly with hepatocellular carcinoma in rodents and has also been described in rats exposed to other carcinogens such as *p*-dimethylaminoazobenzene. Hepatocellular tumors have also been reported in rodents after exposure to DDT, dieldrin, mirex, and Kepone, but these compounds do not produce the same type of liver pathology as PCBs. It is not known whether the experimental hepatic porphyria induced by these compounds is in any way related to the induction of hepatocellular carcinoma. Kepone and technical hexachlorobenzene have been reported to cause hyperplasia of the adrenal cortex in rats and quail. All of the above halogenated organic compounds are persistent in biologic systems, but it is not known whether the isomers that persist are the ones that are carcinogenic. Neoplastic nodules are considered to represent part of the spectrum of response elicited by hepatocarcinogens in rodents. All of the halogenated organic compounds may either prevent or enhance tumor induction by other chemicals. Most of these compounds also require activation so that dermal application would not necessarily result in tumor formation. (15 refs)

- 79-6006 Toxicity and Metabolism of Phthalate Esters. (Eng) Daniel, J. W. (Life Science Res., Stock, Essex, CM4 9PE, England). *Toxicol Annu* 3: 257-268; 1979.

The acute, subacute, and chronic toxicities of the phthalate esters, their effects on reproduction, their carcinogenicities and

mutagenicities, the effects of di(2-ethylhexyl)phthalate (DEHP) on hepatic function and enzyme activity, the absorption, tissue distribution, and excretion of DEHP, and the biotransformation of phthalate esters and their effects on cells in culture are reviewed. Chronic feeding studies suggest that the phthalate esters are not tumorigenic, although both DEHP and dimethoxyethyl phthalate were somewhat mutagenic for male mice following ip administration. DEHP and butylglycolylbutyl phthalate also caused significant growth inhibition in human WI-38 cells in culture. (37 refs)

- 79-6007 Formation of Chemically Reactive Metabolites from Drugs. (Eng) Corcoran, G. B. (Dept. Medicine, Lipid Res. Inst., Baylor Coll. Medicine, Houston, TX 77030); Mitchell, J. R.; Vaishnav, Y.; Horning, E. C.; Nelson, S. D. *Adv Pharmacol Ther* 9: 103-111; 1979.

The pathogenetic role of chemically reactive metabolites in drug-induced tissue lesions is reviewed. At least three types of reactive species causing tissue lesions can be postulated: electrophilic cations showing significant glutathione conjugation in vivo; electrophilic cations not showing glutathione conjugation in vivo; and radicals whose toxicity is potentiated by vitamin E-deficient diets. The initial event in the production of a hepatotoxic arylating metabolite of acetaminophen and phenacetin appears to be N-hydroxylation of the parent drug to N-hydroxyacetaminophen (N-HAA), which spontaneously dehydrates to yield acetimidoquinone, a known arylating agent. Data are consistent with a possible base-catalyzed decomposition of N-HAA through the 1,6-elimination of the elements of water to give acetimidoquinone. N-HAA reacts chemically with L-cysteine, N-acetylcysteine, and glutathione. N-HAA was more potent than acetaminophen in producing hepatic necrosis following ip or iv administration to adult male Swiss mice. The data provide strong evidence that N-HAA, in its dehydrated acetimidoquinone form, is the ultimate hepatotoxic metabolite of acetaminophen. (26 refs)

- 79-6008 Concluding Remarks. (Eng) Gillette, J. R. (Lab. Chemical Pharmacology, Natl. Heart, Lung and Blood Inst., NIH, Bethesda, MD 20014). *Adv Pharmacol Ther* 9: 139-148; 1979.

Conclusions regarding the mechanisms of toxicity of compounds such as phenacetin and N-hydroxy-2-acetylaminofluorene are reviewed. Chemically reactive metabolites may be formed by many different reactions catalyzed by several different enzymes. However, a given enzyme may catalyze not only those reactions leading to toxic metabolites but also to those leading to innocuous metabolites. Similar or identical chemically reactive metabolites of a foreign compound may be formed by different pathways, and the effect of changing the activity of the conjugation system depends on which pathway predominates in a given species. A compound frequently decomposes to several different products, and the formation of some of these products may occur through the sequential formation of several chemically reactive intermediates. A given kind of reaction does not always lead to metabolites that are unstable under physiological conditions. The formation and fate of the reactive metabolites of foreign compounds in enzyme preparations depend on both the enzyme composition of the preparation and the cofactors added to it. It appears that chemically reactive metabolites initiate cancer by becoming covalently bound to target purine bases in DNA to form adducts that cannot be properly replicated. Damage to bacterial DNA may apparently occur even when covalent binding of a

mutagen to DNA is low or absent. Thus, much of the correlation observed between mutagenesis and carcinogenesis may be fortuitous. (28 refs)

- 79-6009 Leukemias and Lymphomas Associated with the use of Cytotoxic and Immunosuppressive Drugs. (Eng) Penn, I. (Dept. Surgery, Univ. Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO 80262). *Recent Results Cancer Res* 69: 7-13; 1979.

A prospective survey was conducted of patients in the Denver area to ascertain the incidence and types of leukemias and lymphomas in those groups receiving immunosuppressive therapy in connection with organ transplantation (800 patients, 526 excluding those with nonmelanoma skin cancers and carcinoma in situ of the cervix), and those receiving cytotoxic agents for cancer chemotherapy (321 patients). Recipients of organ transplants were subject to daily azathioprine plus an adrenal steroid or, alternatively, cyclophosphamide, antilymphocyte globulin, splenectomy and thoracic duct drainage. The incidence of lymphomas among the 526 transplant recipients was 32%, compared with 3%-4% in the general population. The lymphomas appeared after an av of 27 mo of treatment (range 2-146 mo), and the predominant type was reticulum cell sarcoma (105 recipients). Hodgkin's disease was relatively rare (3 recipients). The CNS was involved in 42% of patients with non-Kaposi lymphomas. The incidence of leukemias in transplant recipients was not increased significantly by immunosuppressive therapy; leukemias appeared at an av of 57 mo (range 17-154 mo), and the predominant type was chronic or acute myeloid (57% of 21 cases). A total of 333 new tumors developed in the 321 cancer patients receiving antineoplastic therapy (melphalan, cyclophosphamide and busulfan). The new malignancies were predominantly leukemias (52%) and lymphomas (16%). The leukemias appeared an av of 51 mo after chemotherapy, and the majority were acute myeloblastic (46%), acute myelomonoblastic (27%), or acute erythroleukemia (6%). It was not determined whether the lymphomas in the chemotherapy group represented the spontaneous transformation of one malignancy to another type or were complications of therapy. (12 refs)

- 79-6010 Comparison of Carcinogenicity Studies with Aldrin and Dieldrin. (Eng) Ritper, D. L. (Office Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC 20460). *J Assoc Off Anal Chem* 62(4): 900-903; 1979.

The methodologies used in six carcinogenicity studies of aldrin and dieldrin are reviewed and compared. Three of the studies showed essentially no relationship between dietary aldrin-dieldrin and cancer in the albino rat over periods of 2 yr or more. The other three studies, two of which used mice and one of which used rats, showed a positive correlation between aldrin-dieldrin (10-150 ppm, depending on the study) and tumor (benign or malignant) incidence. Cross-comparison of these six studies showed no clear reason why the animals in some experiments developed tumors and those in other experiments did not. Had more information been provided on the external and/or internal parameters of testing, perhaps some otherwise obscure cause and effect relationships in these studies could have been identified. (7 refs)

- 79-6011 The Identification and Control of Occupational Bladder Cancer. (Eng) Parkes, H. G. (Health Res. Unit, British Manufacturers' Assoc. Ltd., Scala House, Holloway Cir-

cus, Birmingham B1 1EQ, England). *IARC Sci Publ* (25): 47-58; 1979.

The discovery, control, prevention, treatment, and compensation of bladder cancer among workers in the British rubber industry are reviewed. Published case reports from many countries suggested the carcinogenicity of 1- or 2-naphthylamine and benzidine early in the 20th century. The carcinogenicity of 2-naphthylamine was established by laboratory experiments in dogs in 1938, yet the production and use of the chemical continued without controls for another 10 yr. A 1958 epidemiological study of the incidence of bladder cancer in rubber industry workers finally led to discontinuation of the manufacture of this chemical. Strict regulations for the manufacture of benzidine were introduced at the same time. In order to prevent industry-induced cancer, continuous epidemiological surveillance is recommended. Follow-up tests of suspected agents in laboratory animals are necessary to identify causal agents. Workers exposed to carcinogens must have the benefit of regular medical screening programs. Computer technology for correlating data on an international scale may allow early identification and recognition of the carcinogenic potential of chemicals in the working environment. (9 refs)

- 79-6012 The Problem of Measurements Near the Limit of Detection. (Eng) Crummett, W. B. (Analytical Lab., Dow Chemical Co., Midland, MI 48640). *Ann NY Acad Sci* 320: 43-47; 1979.

The problems involved in measuring trace impurities and contaminants near the limit of detection are reviewed. One of the most urgent and highly visible problems in product quality is the reduction of the dioxin content in chlorinated phenolic products. Although the presence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in 2,4,5-trichlorophenol and its derivatives is generally thought to be unavoidable, TCDD has never been conclusively demonstrated in one such derivative, Ronnel. Two highly specific methods have been developed to detect 1 ppb of the carcinogen bis-chloromethyl ether in air. Although a similar method showed the presence of the carcinogen in unsafe quantities whenever formaldehyde and hydrogen chloride were present together in air, a more specific method disproved this finding. Thus, results obtained with the finest equipment and best methods may prove misleading, and the continuous application of the best analytic science is needed to cope with the problems of workplace and environmental contamination. A minimum set of criteria should be developed to assure the integrity of such analytic methodology. Questions designed to help establish precise criteria are presented. These questions relate to methods for sampling, method validation, collaboration, limits of detection, and proof of identity. (18 refs)

- 79-6013 Genetic Effects of Acridine Compounds. (Eng) Nasim, A. (Div. Biological Sciences, Natl. Res. Council Canada, Ottawa, Ontario, Canada); Brychcy, T. *Mutat Res* 65(4): 261-288; 1979.

The biological effects of acridine compounds are reviewed. Acridines and a large number of their derivatives are used in enormous quantities in medicine and industry. The mutagenic activities of these compounds have been demonstrated in many organisms and are known to occur in the dark as well as in the presence of light (photodynamic action). At the molecular level, acridines have been shown to cause frameshift mutations of both the addition

and deletion types. These effects have been of great help in elucidating the nature of the genetic code. Other biological effects of acridines include the inhibition of DNA repair, curing of plasmids, and cell-growth inhibition. (241 refs)

- 79-6014 DNA Binding and Polycyclic Hydrocarbon Carcinogenesis. (Eng) Grover, P. L. (Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England); Sims, P. *Adv Pharmacol Ther* 9: 13-27; 1979.

The role of DNA binding in polycyclic hydrocarbon (PCH) carcinogenesis is reviewed. The first step in the metabolism of an unsubstituted PCH such as benzo(a)pyrene (BP) is the formation of a simple epoxide, a reaction catalyzed by the NADPH-dependent microsomal monooxygenases. These simple epoxides can then: rearrange nonenzymically to phenols; be hydrated to give dihydrodiols, a reaction catalyzed by microsomal epoxide hydratase; or be conjugated with glutathione, a reaction catalyzed by soluble glutathione transferases. There is evidence that the formation of vicinal diol epoxides is a general mechanism of activation applicable to the PCH's as a class of chemical carcinogens. The most reactive diol epoxides of this type are probably those in which the epoxide grouping is adjacent to a "bay region." The following PCH's are metabolically activated through their conversion of vicinal diol epoxides that react with nucleic acids: BP, benz(a)anthracene, 7-methylbenz(a)anthracene, 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene. (82 refs)

- 79-6015 Biological Activity of Polycyclic Hydrocarbon Metabolites and the Bay Region Theory. (Eng) Conney, A. H. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110); Levin, W.; Wood, A. W.; Yagi, H.; Lehr, R. E.; Jerina, D. M. *Adv Pharmacol Ther* 9: 41-52; 1979.

The bay region theory of polycyclic hydrocarbon (PCH) carcinogenesis is reviewed, as are the biological activities of metabolites of benzo(a)pyrene (BP), benz(a)anthracene (BA), dibenz(a,h)anthracene (DBA), and chrysene. The proximate carcinogenic metabolites of BP appear to be BP 7,8-oxide and BP 7,8-dihydrodiol, whereas BP 7,8-diol-9,10-epoxide-2 is an ultimate carcinogenic metabolite in the neonatal mouse. A saturated benzo ring and a bay region 9,10-epoxide group appear to be required for high biological activity of BP. BA 3,4-dihydrodiol is a proximate carcinogenic metabolite of the weak carcinogen BA, and BA 3,4-diol-1,2-epoxide-2 is an ultimate carcinogenic metabolite. The bay region theory predicts that one or more of the DBA 3,4-diol-1,2-epoxides are ultimate carcinogenic metabolites of DBA, and experimental data indicate that the 3,4-dihydrodiol of DBA is significantly tumorigenic for mouse skin and neonatal mice. Chrysene 1,2-dihydrodiol is a proximate carcinogenic metabolite of chrysene, and chrysene 1,2-diol-3,4-epoxide, in which the epoxide group is in the bay region of the molecule, is probably an ultimate carcinogenic metabolite of chrysene. Every hydrocarbon examined to date has been shown to meet the predictions of the bay region theory. (53 refs)

- 79-6016 Carcinogenic Chemicals in the Environment. (Nor) Aune, T. (Miljøtoksikologisk avdeling, Statens Institutt for Folkehelse, Oslo, Norway). *Kjemi* 39(5): 25-29; 1979.

Recent studies on environmental carcinogens are reviewed. The chemical substances known to be carcinogenic in humans include aflatoxins, 4-aminobiphenyl, arsenic compounds, substances occurring in the synthesis of auramine, benzene, benzidine, bis(chloromethyl) ether, cadmium, chloramphenicol, chloromethyl methyl ether, chromium, cyclophosphamide, diethylstilbestrol, isopropyl oils, Melphalan, mustard gas, 2-naphthylamine, nickel, N,N-bis(2-chloroethyl)-2-naphthylamine, oxymetholone, phenacetin, soot, tar, and vinyl chloride. The mutagenicity of cigarette smoke condensate cannot be explained with the presence of benzo(a)pyrene and nitrosamines alone. There are strong indications that the pyrolysis products of proteins and amino acids contribute substantially to the mutagenic effect. It cannot be ruled out that such cocarcinogens as harman and norharman also play an important role. Chemically induced cancer is dose-dependent, even though the dose-response relationship for humans is not yet known for the concentrations that are relevant for human exposure. The fact that a chemical induces cancer in animals or mutations in other test systems is not always sufficient substantiation for the ban of that substance. (6 refs)

- 79-6017 Stereoselective Metabolic Activation of Polycyclic Aromatic Hydrocarbons. (Eng) Jerina, D. M. (Section Oxidation Mechanisms, Lab. Chemistry, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014); Yagi, H.; Thakker, D. R.; Karle, J. M.; Mah, H. D.; Boyd, D. R.; Gadaginamath, G.; Wood, A. W.; Buening, M.; Chang, R. L.; Levin, W.; Conney, A. H. *Adv Pharmacol Ther* 9: 53-62; 1979.

The most extensively formed and most biologically active stereoisomers of the polycyclic aromatic hydrocarbons are reviewed. The metabolism of benzo(a)pyrene (BP) by rat liver microsomes is highly stereoselective in the formation of (-)-BP 7,8-dihydrodiol, this enantiomer being 5- to 10-fold more potent than the (+)-enantiomer as a tumor initiator and complete carcinogen in CD-1 mice and 10- to 20-fold more active than BP or the (+)-enantiomer in causing pulmonary adenomas and lymphomas in these animals. Of the four possible BP 7,8-diol-9,10-epoxides, the two that are formed most extensively from BP by liver are the two that are found bound to the nucleic acid of the target tissue. One of these isomers, (+)-diol epoxide-2, is 6- to 18-fold more mutagenic for Chinese hamster V79 cells than the other three, and it is more tumorigenic for newborn Swiss-Webster mice. The (-)-enantiomer of BP 4,5-oxide is sixfold more mutagenic toward V79 cells than the (+)-enantiomer. The more tumorigenic (-)-(3R,4R)-enantiomer of benz(a)anthracene is the major enantiomer formed by rat liver microsomes from the parent compound. (36 refs)

- 79-6018 Toxicologic Properties of Fluorescent Whitening Agents. (Eng) Gloxhuber, C. (Henkel KGaA, Dusseldorf, W. Germany); Bloching, H. *Toxicol Annu* 3: 171-203; 1979.

The toxicologic properties of the fluorescent whitening agents (FWA's) used in soaps, detergents, and textile finishing are reviewed. Topics discussed include extent of human exposure; metabolism and excretion; acute and chronic toxicity; dermal irritation; mucous membrane irritation; effects on wound healing; sensitizing properties; phototoxic and photoallergic properties; effects on blood coagulation; estrogenic properties; carcinogenicity; embryotoxicity; and mutagenicity. Few or no changes were observed following repeated sc or po administration of numerous FWA's to cats, rats, rabbits, dogs, or monkeys. Similarly, various

FWA's were noncarcinogenic following po, sc, or topical administration to mice, and none of the compounds tested showed evidence of photocarcinogenicity or teratogenicity. Some FWA's induced petite mutations in *Saccharomyces cerevisiae* in the dark, but none were mutagenic for *Salmonella typhimurium* or warm-blooded animals. No pathologic changes were observed after administration of FWA's to fish, and FWA's did not reach the edible parts of fish. (62 refs)

- 79-6019 Is the Cancer Process Caused by Deletion of One or More Differentiation Genes Normally Activated by Steroid Hormones? (Eng) Money-Kyrle, A. F. (Whetham, Calne, Wilts, England). *Med Hypotheses* 5(9): 987-994; 1979.

The possibility that cancer is caused by the deletion of a gene(s) normally activated by steroid hormones is discussed, and relevant literature is reviewed. It is hypothesized that aflatoxin B₁ and polycyclic hydrocarbon carcinogens cause the deletion of genes necessary for the production of a substance required for the differentiation of the cell and activated by a steroid hormone (possibly a corticosteroid). Such genes could include genes for the production of glutamine transaminase and glutamine synthetase and those involved in vitamin A metabolism. Deletion of any of these genes could cause the cell to remain in an undifferentiated and replicating state. A carcinogen may combine chemically with a gene necessary for cell differentiation, after which a tumor promoter may unmask genes that allow cell division. The gene that had combined chemically with the carcinogen would then be unable to divide; as a result, the progeny would not contain the gene and would be unable to differentiate. (31 refs)

- 79-6020 Metabolic Activation of Chemicals to Reactive Electrophiles: An Overview. (Eng) Miller, J. A. (McArdle Lab. Cancer Res., Center Health Sciences, Univ. Wisconsin, Madison, WI 53706); Miller, E. C. *Adv Pharmacol Ther* 9: 3-12; 1979.

The metabolic activation of chemicals to reactive electrophiles is reviewed. Most chemical carcinogens and most drugs that yield covalent interactions in vivo are unreactive per se and must be activated metabolically to form strong nucleophilic reactants. The electrophilic forms of chemical carcinogens appear to be involved in the initiation of carcinogenesis, and they may also participate in the promotion phase; the same or different metabolites of a complete carcinogen may be involved in these two stages. The metabolism of the following compounds to reactive, mutagenic, and carcinogenic electrophiles is described: aromatic amines, amides, and nitro compounds; aflatoxin B₁; safrole and related allylic benzenes; and ethyl carbamate. (28 refs)

- 79-6021 In Vivo Covalent Binding of Organic Chemicals To DNA as a Quantitative Indicator in the Process of Chemical Carcinogenesis. (Eng) Lutz, W. K. (Inst. Toxicology, Swiss Federal Inst. Technology, Univ. Zurich, CH-8603 Schwerzenbach, Switzerland). *Mutat Res* 65(4): 289-356; 1979.

The use of in vivo covalent binding of organic chemicals to DNA as a quantitative indicator in the process of chemical carcinogenesis is reviewed. A detailed description of the planning and performance of a DNA-binding assay is given, as is a complete literature survey of the in vivo DNA binding of 83 compounds.

REVIEW

The Covalent-binding Index (CBI) is calculated where possible. A list is also provided of 153 compounds that have shown covalent binding to any biological macromolecule in vitro or in vivo. Recent unpublished studies with aflatoxin M₁, macromolecule-bound aflatoxin B₁, stilbestrol, and 1,2-epithiobutyronitrile are included. The CBI for rat-liver DNA showed a surprisingly good quantitative correlation with hepatocarcinogenic potency. Refinements for a DNA-binding assay are proposed, and possibilities and limitations of the use of DNA binding in chemical carcinogenesis are discussed. (295 refs)

- 79-6022 Nutrition and Cancer: A Review. (Eng) Doll, R. (Radcliffe Infirmary, Univ. Oxford, Oxford, England). *Nutr Cancer* 1(3): 35-45; 1979.

The ways in which food and drink can contribute to, or prevent, the development of cancer are reviewed. The consumption of alcohol is associated with an increased risk of cancer of the mouth, pharynx, larynx, and esophagus in many countries, different types of alcoholic beverages sometimes having effects independent of the quantity consumed. Aflatoxin consumption appears to be related to liver cancer, and overnutrition (obesity) is related to cancers of the colon, rectum, breast, and endometrium. The effect, if any, of overnutrition is probably related to the specific effects of individual nutrients. Fat consumption is closely correlated with cancer of the endometrium, breast, and colon, and the consumption of meat, particularly beef, is associated with colon cancer. Vegetables may have a protective effect against colon cancer, as may dietary fiber. It has been hypothesized that differences in diet may act by modifying the bacterial flora in the gut, particularly in one group of clostridia capable of dehydrogenating steroid nuclei. Relative deficiencies of vitamins and trace elements have been suggested as contributing to cancer, and there is some evidence that nitrosatable compounds may contribute to gastric cancer. Bracken fern, which is a common food item in Japan, is associated with esophageal cancer, and smoked and grilled foods may be related to gastric cancer. Neither laboratory nor epidemiological data have linked any food additives to human cancer. (82 refs)

- 79-6023 Chemical Characterization of 465 Known or Suspected Carcinogens and Their Correlation with Mutagenic Activity in the *Salmonella typhimurium* System. (Eng) Rinkus, S. J. (Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX 77550); Legator, M. S. *Cancer Res* 39(9): 3289-3318; 1979.

The chemical characterization of 465 known and suspected carcinogens is reviewed, as are the mutagenicities of these compounds in the *Salmonella typhimurium* system. No attempt was made to distinguish truly carcinogenic chemicals from promoters and solid-state carcinogens. About 58% of the 465 compounds were adequately tested in *Salmonella*. On the basis of recurring chemical structures, the compounds could be divided into 39 separate categories. The most salient common feature among the 210 compounds that were mutagenic for *Salmonella* was an electrophilicity that was intrinsic to the molecule or introduced by enzymatic modification. Only a few intrinsically electrophilic carcinogens were not active in the *Salmonella* test. Poorly detected categories of carcinogens included: azanaphthols; carbamyls and thiocarbamyls; phenyls; benzodioxoles; polychlorinated aromatics, cyclics, and aliphatics; steroids; antimetabolites; and symmetrical

hydrazines. Nonstandard procedures were necessary to optimize the testing of chemicals that were bactericidal or volatile or that cross-linked DNA. False negatives appeared to arise for two reasons: an inability to devise an in vitro activation system that could be reliably used in a standard way, and an inability to detect the entire spectrum of mutational events that can lead to cancer induction. (255 refs)

- 79-6024 Metabolic Activation of Aminostilbene Derivatives and Diethylstilbestrol. (Eng) Neumann, H. G. (Inst. Pharmacology and Toxicology, Univ. Wurzburg, 87 Wurzburg, W. Germany); Metzler, M. *Adv Pharmacol Ther* 9: 113-122; 1979.

The metabolic activation of aminostilbene derivatives and diethylstilbestrol (DES) is reviewed. α,β -Dihydroxy-acetylaminobenzyl has been identified as the major metabolite of *trans*-4-dimethylaminostilbene (*trans*-DAS), and it was proposed that an epoxide is formed at the stilbene double bond. The metabolic activation of *trans*-DAS appears to be dose-independent, and reactive metabolites are formed in the liver and distributed in the circulation. The evidence suggests that a pharmacokinetic threshold does not exist for *trans*-DAS. Epoxidation of the stilbene bond may also represent a major metabolic pathway for DES. Another major metabolite in most species results from the oxidation of the aliphatic side chain. β -Dienestrol is also a major metabolite in most species. (34 refs)

- 79-6025 The Effects of Exogenous Female Hormones on the Fetus. (Eng) Shapiro, S. (Drug Epidemiology Unit, Boston Univ. Sch. Medicine, 777 Concord Ave., Cambridge, MA 02138); Slone, D. *Epidemiol Rev* 1: 110-123; 1979.

The evidence linking the use of female hormones to various effects in the human fetus is reviewed. These effects include malformations, abortion, prematurity, perinatal mortality, and neoplasia. Clear cell adenocarcinomas of the vagina and cervix in female offspring have been associated with maternal use of diethylstilbestrol (DES) during pregnancy, especially during the first trimester. The incidence of these neoplasms attributable to DES is between 0.1 and 1 per 1,000 up to 22 yr of age. Vaginal epithelial changes in the offspring, including adenosis, have also been associated with DES use by their mothers during pregnancy. There is some evidence that DES use may be associated with testicular cancer in male offspring. There is as yet no more than anecdotal evidence that DES is related to cancers at sites other than the female genital tract in exposed female offspring, and other estrogens and progesterone have not been exonerated in the genesis of clear cell adenocarcinomas in exposed offspring. (66 refs)

- 79-6026 Susceptibility to Cancer and the Influence of Nutrition. (Eng) Sabine, J. R. (Dept. Animal Physiology, Univ. Adelaide, Waite Agricultural Res. Inst., Glen Osmond, S.A. 5064, Australia). *Nutr Cancer* 1(3): 52-57; 1979.

The influence of nutrition on susceptibility to cancer development is reviewed. Experiments, especially those employing animals, designed to relate nutritional factors to cancer incidence must take into account several critical theoretical and practical considerations. At the theoretical level, susceptibility to cancer is a combination of genetic, physiological, and metabolic factors, and any one

or all of these may be influenced by nutritional variables. Similarly, the development of cancer in any one individual is a progressive event and it must be recognized that diet may influence any one or more of these stages. At the practical level, problems can arise because any experiment with animals is also a nutritional experiment; in addition, different answers to the same nutritional question can be obtained simply by choosing different experimental tumor models. Some experiments have shown vitamin A to have a prophylactic and/or therapeutic effect on certain premalignant and malignant lesions, whereas other investigations have shown no correlation between serum vitamin A levels and histologic subtype, extent of disease, or presence or absence of metastases. With regard to dietary fat, experimental data have suggested everything from a close association with cancer etiology to no association. In contrast, the current evidence is generally compatible with the suggestion that there is a fundamental and functional link between cholesterol status, particularly subnormal cholesterol levels, and cancer. It is no longer sufficient just to feed experimental animals and tabulate deaths; the intervening steps must be measured. (17 refs)

- 79-6027 Prolactin and Mammary Cancerigenesis. (Eng) Welsch, C. W. (Dept. Anatomy, Michigan State Univ., E. Lansing, MI 48824); Meites, J. *Prog Cancer Res Ther* 9: 71-92; 1978.

A crucial role for pituitary prolactin in the development and growth of rodent mammary cancers has been demonstrated in several studies. In certain endocrinological states, chronic hyperprolactinemia in susceptible strains of mice and rats can invariably enhance mammary tumorigenesis. In other endocrinological states, hyperprolactinemia can actually inhibit this process in both mice and rats. Chronic hypoprolactinemia, on the other hand, can cause regression of existing rat mammary cancers and, under certain conditions, it can suppress or prevent the development of these neoplasms in mice. Therefore, prolactin is a key hormone during carcinogenesis in the rodent mammary gland. Whether or not prolactin is of significant importance in human breast carcinogenesis remains to be determined. If prolactin can be shown to influence human breast epithelium in a manner similar to its effect on rodent mammary tissue, prophylactic and/or chemotherapeutic control of human breast cancer development may be feasible by appropriate drug-mediated prolactin suppression. (139 refs)

- 79-6028 Steroid Hormone Action in Uterine Cancer. (Eng) Takamizawa, H. (Dept. Obstetrics and Gynecology, Chiba Univ. Sch. Medicine, Inohana, Chiba 280, Japan); Sekiya, S. *Prog Cancer Res Ther* 9: 233-247; 1978.

Recent advances in studies of the effects of sex steroids on the development of endometrial carcinoma are reviewed. Unopposed exposure of uterine endometrium to estrogen has been considered a causal factor in the development of adenocarcinoma. Although a carcinogenic potential for estrogen has not been proved, excess extraglandular production of estrone appears to be common in women at high risk for endometrial hyperplasia and carcinoma. Synthetic progestational agents are effective in about one-third of patients with advanced endometrial carcinoma. Direct action by hormones is suggested by in vitro studies, and the effect may be provoked by intracellular receptors, as is observed in normal progenitor cells. Several studies indicate that the progesterone receptor is gradually lost during malignant transformation of the endometrium. (139 refs)

- 79-6029 Diet and Hormones in the Epidemiology of Breast and Endometrial Cancers. (Eng) Armstrong, B. K. (Public Health Dept., Perth, W. Australia). *Nutr Cancer* 1(3): 90-95; 1979.

The roles of diet and hormones in the epidemiology of breast and endometrial cancer are reviewed. These cancers are closely associated geographically, show similar changes in incidence with age, and share some indicators of individual risk. There is evidence that hormones are involved in the etiology of both diseases. Evidence for the association between estrogens and endometrial cancer is strong, but the associations between estrogens, prolactin, and breast cancer are weak. Diet may also be involved in the etiology of breast and endometrial cancers. There may be an association between excess dietary fat and breast cancer risk and between obesity and endometrial cancer risk. Obesity, and therefore excess dietary energy, increases the endogenous production of estrogens. Dietary fat per se may increase both estrogen and prolactin production. It appears likely, therefore, that the influence of diet on the risk of breast and endometrial cancers is mediated through changes in the levels of these hormones. (67 refs)

- 79-6030 Theoretical Mechanisms for Synthesis of Carcinogen-induced Embryonic Proteins. V. The Steroids. (Eng) Hancock, R. L. (High River Inst. Theoretical Cancer Study, High River, Alberta, Canada); Payette, R. *Med Hypotheses* 5(10): 1145-1167; 1979.

The embryonic features of neoplastic cells induced by steroids are reviewed, and a mechanism for this phenomenon is postulated. Estrogen receptor complexes and their effects on chromatin proteins are discussed in detail. A mechanism for the action of estradiol-17- β , in particular for its ability to alter the gene expression (derepression) of mammary gland epithelial cells, is presented. (60 refs)

- 79-6031 A Possible Role of Estrogens in Carcinogenesis of Non-Target Tissues. (Eng) Litvay, M. (75 Kendal Ave., Toronto, Ontario M5R 1L8, Canada). *Med Hypotheses* 5(9): 953-968; 1979.

Information concerning the possible role of estrogens in carcinogenesis of nontarget tissue is reviewed. The mitogenic action of the estrogen-receptor complex is apparently similar in both normal and malignant target tissues. Receptors are also present in several types of non-target tissues, and complexes in those tissues might cause successive mitoses. In normal and malignant cells of the breast and some other types of nonendocrine cells, the ability to produce estrogens from circulating precursors has been demonstrated. These locally formed estrogens might play a role in the initiation of some types of malignant transformation. Indications of such a process include the switching to estrogen production in some neoplastic endocrine or undifferentiated cells; certain ectopic effects displayed by some cancerous tissues; and the existence of evidence that growth hormone, prolactin, and cholesterol are involved in the development of some malignancies. It is hypothesized that the present system for sex hormone synthesis might be an adaptation of a more primitive system in which several cell-types have retained their ability to synthesize these hormones. Polypeptide hormones might evolve from regulatory parts of cyclases or phosphodiesterases. (72 refs)

REVIEW

79-6032 Low-Dose and Species-to-Species Extrapolation for Chemically Induced Carcinogenesis. (Eng) Hoel, D. (Biometry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978.* McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 135-145; 1979.

Statistical procedures currently used for estimating a low-dose carcinogenic effect in humans based on data from animal studies are reviewed. The mathematical models commonly used to show dose-response relationships generally fall into one of two categories: they may focus on a dichotomous response (eg, the one-hit and probit models); or they may attempt to relate the distribution of the time until occurrence of a given event to dose level (eg, the log-normal and Weibull models). Although the probit and related curves tend to provide similar fits to experimental data, they can generate risk estimates that differ by as much as threefold when extrapolating to incidence rates in the 10^4 and 10^6 range. Thus, it is important to develop a rational basis for selecting among competing extrapolating models. The assumption of linearity of response in the low-dose range appears to be conservative, based on quantitative deductions. The importance of background levels and the manner in which corrections are made for them can have a significant effect on estimated risk. Even greater quantitative errors in risk assessment are probably associated with species scale-up than with the dose-response models. The units in which the dose rate is expressed in the estimation of relative human risk are of great importance. Industrial exposures are generally limited to only a fraction of an individual's total life span, and the manner in which cumulative tumor incidence is adjusted to reflect a lack of lifetime exposure data can significantly alter risk estimates. (7 refs)

79-6033 Setting Tolerances on the Basis of Mathematical Treatment of Dose-Response Data Extrapolated to Low Doses. (Eng) Cornfield, J. (Dept. Statistics, George Washington Univ., Washington, DC); Carlborg, F. W.; Van Ryzin, J. In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977.* Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 143-164; 1978.

The use of dose-response data mathematically extrapolated to low doses for the determination of tolerance levels is reviewed. The dose-response curve derived from the kinetics of a well-understood detoxification reaction is discussed. With such a nonthreshold model, any nonzero dose is treated mathematically as leading to some increased probability of a response. Setting a tolerance requires specifying an acceptable risk. Some standard dose-response curves are discussed, as are the joint effects of many agents and the extrapolation of animal data to human risk. (47 refs)

79-6034 Review of In Vitro Test Systems Using DNA Damage and Repair for Screening of Chemical Carcinogens. (Eng) Williams, G. M. (American Health Foundation Disease Prevention, Naylor Dana Inst., 1 Dana Rd., Valhalla, NY 10595). *J Assoc Off Anal Chem* 62(4): 857-863; 1979.

In vitro test systems using DNA damage and repair for screening chemical carcinogens are reviewed. A mechanistic classification of

chemical carcinogens separates them into two categories: genotoxic (carcinogens that interact directly with DNA), and epigenetic (carcinogens which operate by other mechanisms). Since most in vitro tests for chemical carcinogens have as their indicators some genotoxic effect, not all chemical carcinogens will give positive results in such tests. Also, because no single test detects all genotoxic carcinogens, it is necessary to have a battery of short-term tests. Tests for overall damage are the most broadly sensitive for the detection of DNA damage, but they are redundant when paired with bacterial mutagenesis tests. DNA repair has also been advocated as a screening test, but only excision repair has application to carcinogen screening. The most widely used techniques for monitoring repair measure resynthesis of the excised damaged segments of DNA. Autoradiographic measurement of unscheduled DNA synthesis remains the simplest technique and one for which no failure of correlation with DNA repair has been reported. DNA repair is a greater indicator of damage than cell toxicity or death and would be of greater value as part of a battery of tests. DNA repair is also superior in this respect to the Painter test. The hepatocyte primary culture/DNA repair test has great potential as part of a screening battery. It is broadly sensitive to a variety of structurally different types of carcinogens requiring metabolic activation, and it provides intracellular metabolism in an intact mammalian cell. (64 refs)

79-6035 Cytogenetic Studies and Risk Assessment for Chemicals and Ionizing Radiation. (Eng) Brewen, J. G. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978.* McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 97-115; 1979.

The role of structural chromosome aberrations (SCAs) in risk assessment for chemicals and ionizing radiation is reviewed. SCAs constitute a major component of the genetic damage produced by practically any mutagenic insult in higher eukaryotic systems. Data relating to the molecular mechanism of aberration formation in higher cells can be used for making qualitative and quantitative risk estimates for humans or mice. (27 refs)

79-6036 Overview and Status of In Vitro Transformation. (Eng) Sivak, A. (Bio/Medical Sciences Section, Arthur D. Little, Inc., Cambridge, MA 02140). *J Assoc Off Anal Chem* 62(4): 889-899; 1979.

The status of in vitro transformation assays for the detection of chemical carcinogens is reviewed. In vitro cell culture systems fall generally into three classes: diploid cell strains, Syrian hamster embryo cells; cell lines, mouse BALB/c-3T3 and mouse C3H-10T1/2 cells; and cells plus virus, Fischer rat cells infected with Rauscher leukemia virus and Syrian hamster embryo cells infected with adenovirus. The data accumulated to date show a good correlation between the transformation response in cell culture and the carcinogenicities of chemicals in whole animal studies. The major advantages of the cell culture systems are their relatively small time and cost requirements and their relevance to the carcinogenic process. Their disadvantages are the uncertain nature of the metabolic capabilities of the target cells and the lack of a reliable metabolic activation system that is adaptable for routine bioassays. The development of epithelial cell systems may solve the problem of

carcinogen metabolism as well as provide target cells that are representative of the major organ sites for human cancer. (36 refs)

- 79-6037 Crown Gall Disease. (Eng) Drummond, M. (ARC Unit Nitrogen Fixation, Univ. Sussex, Falmer, Brighton, England). *Nature* 281(5730): 343-347; 1979.

The induction of crown gall disease in plants by *Agrobacterium tumefaciens* is reviewed. *A. tumefaciens* induces this plant tumor by transferring part of a large bacterial plasmid (Ti plasmid) to the plant cells. Crown gall tissue synthesizes opines, which serve as a carbon or nitrogen source for the oncogenic bacteria. The nature of the opine produced is determined by the bacterium and is the one catabolized by the inducing strain. Ti plasmids promote bacterial conjugation and the genes required for their transfer are closely associated with opine metabolism. Experiments with restriction fragments containing T-DNA of an octopine plasmid have shown that the left end of the octopine T-DNA and sequences extending as far as its left-hand boundary are highly conserved on all Ti plasmids. The greater part of the conserved region is found in all tumor lines examined and is probably sufficient for tumor maintenance. Oncogenesis could result from the insertion of T-DNA onto host genes crucial to the control of cell division or from the action of a specific oncogenic gene product, analogous to the tumor (T)-antigen of simian virus 40 (SV40)-transformed rodent cells. At least a part of T-DNA is transcribed in the plant cell. Hormone imbalance is also strongly implicated in the etiology of crown gall disease. Crown gall tumors can regain normal morphology under certain conditions, with the reversion taking place at the phenotypic or genotypic level. The author speculates that Ti plasmids may be used as factors to insert a chosen DNA sequence into the genome of any dicotyledonous plant. (79 refs)

- 79-6038 Models of Chemical Hepatocarcinogenesis and Oncodevelopmental Gene Expression. (Eng) Stillman, D. (Dept. Biology, Univ. California at San Diego, La Jolla, CA 92093); Sell, S. *Methods Cancer Res* 18: 135-168; 1979.

The production of oncodevelopmental gene products during exposure of the liver to carcinogens is reviewed. The products discussed include enzymes and isoenzymes, α -fetoprotein (AFP), nonhistone proteins, preneoplastic antigen, and isoferitins. Exposure to hepatocarcinogens leads to progressive morphologic changes in populations of adult liver cells, so that they eventually resemble fetal liver cells. Immunological and biochemical studies have provided evidence that genes that are active during fetal and neonatal development, yet essentially silent in the adult, may be activated during carcinogenesis. Chemical hepatocarcinogenesis involves a series of sequential changes in hepatocyte morphology accompanied by biochemical changes. Production of high levels of AFP, fetal isoenzymes, or other products may precede obvious morphological changes. However, although there is suggestive evidence, it has not been established whether sequential changes in gene expression, as indicated by AFP production and ultrastructural changes, are essential steps prior to malignant transformation. Similarly, although circumstantial evidence exists, there is no formal proof of an evolution of cancer from premalignant nodules or morphologically altered cells. Oncodevelopmental gene products are also expressed in transplantable hepatomas. Each hepatoma expresses a pattern of enzyme activities that is essentially unique for the given tumor. Fetal enzyme activities are commonly expressed, but the overall pattern for any given tumor is different from any given point in the development of the fetal liver. (125 refs)

- 79-6039 Oncodevelopmental Antigen Expression in Chemical Carcinogenesis. (Eng) Rees, R. C. (Cancer Res. Campaign Labs., Univ. Nottingham, Nottingham, England); Price, M. R.; Baldwin, R. W. *Methods Cancer Res* 18: 99-133; 1979.

The available information pertaining to fetal antigens in chemical carcinogenesis is reviewed, along with relevant information from studies using virally induced or spontaneously arising tumor systems. Topics discussed include phase-specific gene products of the fetus and fetal gene expression by adult cells; the expression and occurrence of oncodevelopmental antigens; the characteristics of oncodevelopmental antigens; and the immunogenicities of tumor-associated and oncodevelopmental antigens. (89 refs)

- 79-6040 Mechanisms of Carcinogenesis: Implications and Relevance to the Role of Nutrition in Cancer Causation. (Eng) Stewart, B. W. (Sch. Pathology, Univ. New South Wales, Box 1, Kensington, NSW 2033 Australia). *Nutr Cancer* 1(3): 46-51; 1979.

The role of nutrition in the etiology of cancer is reviewed. The vast majority of chemical carcinogens are metabolized by microsome-associated enzymes and there is a concomitant production of reactive intermediates able to bond covalently with the constituents of normal tissue. Available evidence suggests that binding of carcinogen adducts to DNA is of particular significance. The development of neoplasia is almost invariably associated with continual exposure to a carcinogen(s) and to some stimulus to cell proliferation. There are classes of carcinogens that may occur as dietary contaminants, and it has recently been established that some carcinogens may be formed in the digestive tract from non-carcinogenic components. The activity of enzymes responsible for the metabolism of carcinogens and similar exogenous compounds may be subject to extreme modulation by variations in diet. This dietary influence may be mediated through parameters ranging from the chemical and microbiological environment of the digestive tract to the activity of hepatic microsomal enzymes. Such factors may, in turn, determine the structure and quantity of carcinogenic intermediates to which tissues are exposed. (49 refs)

- 79-6041 Dietary Deficiency of Protein, Amino Acids and Total Calories on Development and Growth of Cancer. (Eng) Jose, D. (Clinical Immunology and Immunogenetics, Cancer Inst., 481 Little Lonsdale Street, Melbourne, 3000, Australia). *Nutr Cancer* 1(3): 58-63; 1979.

The effects of dietary deficiencies of protein, amino acids, and total calories on the development and growth of cancer are reviewed. The major source of information on this subject comes from studies of such deficiencies in experimental systems. Caloric restriction (one-half to one-third control intake) has influenced the genesis of virtually all mouse tumors studied, but only when the low-calorie diets were also low in fat. The extent of the inhibitory effects on tumorigenesis in these studies was related to the duration of the dietary restriction. Diets deficient in protein were associated with a 50% reduction in carcinogen-induced leukemia in DBA mice and a markedly reduced incidence of spontaneous mammary tumors in C3H mice. Selective deficiency of one essential amino acid in the diet inhibited tumor growth in numerous experiments; in most of the experiments in which this effect was measured, there was also a reduction in body wt on these diets. Diets deficient in tyrosine and phenylalanine were also associated

with reductions in metastatic disease and arrests of primary tumor growth in human patients. (46 refs)

- 79-6042 Food Additives. (Eng) Farrer, K. T. (Kraft Foods Limited, Box 1673N, G. P. O., Melbourne, Victoria, 3001, Australia). *Nutr Cancer* 1(3): 100-103; 1979.

Food additives are reviewed with regard to definition, reasons for their use, concentrations used, and control of their use. In Australia, food additives may be used only if specifically permitted to be added to the product in question and then only up to a given concentration. The max concentrations are derived from recommendations by the Joint Expert Committee on Food Additives of the Food and Agricultural Organization/World Health Organization. Acceptable daily intakes for all additives are derived from data on their biochemistry; carcinogenicity, mutagenicity, teratogenicity, etc; their acute, subacute, and chronic toxicity; observations in man; and studies on transformation products or impurities. The final question in the use of food additives is one of risk benefit. (18 refs)

- 79-6043 Introductory Remarks: Consideration of Experimental Thresholds. (Eng) Golberg, L. (Chemical Industry Inst. Toxicology, Research Triangle Park, NC). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 87-95; 1978.

Problems involved in the extrapolation of results from toxicological studies in animals to humans are considered. The organ damage observed at high doses may bear little or no relationship to whatever physiological perturbations may be induced by the same compound at doses to which humans are exposed. Where the traditional high-dose approach is used as part of a dose-response study, knowledge of metabolic pharmacokinetic properties of the test substance permits assessment of the metabolite load at the various doses and facilitates interpretation of the toxicological findings. The concept of relative risk should include an understanding of environmental carcinogens and mutagens present in natural foods. Endogenous factors such as the production of nitrosamines as well as of protective factors (eg, antioxidants) should be given special attention when assessing risk to humans from environmental agents. A balanced approach to statistical extrapolation not only has a place in interpreting likely low-exposure effects from the data obtained with high doses but can yield new insights into the biological process itself. (12 refs)

- 79-6044 Chemical Carcinogenesis in Syrian Hamsters: A Review (Through 1976). (Eng) Homburger, F. (Bio-Res. Inst., Cambridge, MA). *Prog Exp Tumor Res* 23: 100-179; 1979.

The recent literature concerning chemical carcinogenesis in the Syrian golden hamster is reviewed. Summaries and evaluations of published material are provided, along with abstracts, most of which were taken from published papers. Chemical carcinogenesis of the skin, subcutaneous tissue, cheek pouch, oral cavity, tongue, respiratory tract, gastrointestinal tract, liver and biliary tract, kidney, urinary bladder, prostate, ovary and thyroid, testicles,

mammary gland, pancreas, and adrenal is reviewed, as are the effects of inhaled chemical carcinogens. (199 refs)

- 79-6045 Introductory Remarks. (Eng) Munro, I. C. (Toxicology Res. Div., Bureau Chemical Safety, Health and Welfare Canada, Ottawa, Canada). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 165-167; 1978.

The concepts of thresholds and acceptable daily intakes as related to the safety of chemicals in food, drugs, and the environment are reviewed. A major problem facing toxicologists is whether thresholds exist for mutagenic and carcinogenic events in mammalian systems. It has been suggested that no safe dose exists for chemical carcinogens. Before thresholds can be established, the factors affecting them must be determined. The ability of endogenous compounds to trap electrophilic agents and prevent them from reaching their critical targets must also be investigated. With regard to toxic events that occur in low incidence and show wide intertrial variations, it is impossible to identify the biochemical events related to the toxic manifestations. (no refs)

- 79-6046 Environmental Chemicals Causing Cancer and Genetic Birth Defects: Mutagenicity Testing for Reactive Metabolites. (Eng) Ames, B. N. (Dept. Biochemistry, Univ. California, Berkeley, CA 94720). *Adv Pharmacol Ther* 9: 29-40; 1979.

Mutagenicity testing for the reactive metabolites of environmental chemicals causing cancer and genetic birth defects is reviewed. Damage to DNA appears to be the most likely cause of cancer and genetic birth defects. Because of the long tumor latency periods, it is difficult to identify the mutagens and carcinogens causing cancer in humans. Chemicals to which humans are exposed in appreciable amounts should be screened in animal tests, but these tests are expensive, they present statistical problems related to small sample sizes, and they are not usually suitable for identifying the active agent in a complex mixture. Using special strains of *Salmonella* in combination with homogenized mammalian liver tissue, carcinogens and mutagens can be identified by means of their mutagenicity. In a test of several carcinogens and noncarcinogens, 158/176 organic carcinogens were mutagenic and 95/108 noncarcinogens were nonmutagenic. The following chemicals identified by this test as mutagens were subsequently found to be human carcinogens: furylfuramide, ethylene dichloride, 1,2-dibromoethane, tris-(2,3-dibromopropyl)phosphate, and most common hair dyes. Since the development of the *Salmonella* test, there has been a resurgence of interest in other short-term mutagenicity tests. Because each of these tests detects a few carcinogens that the others do not, the concept of a battery of short-term tests is favored. A knowledge of carcinogenic potency, which can be gained by both animal cancer and short-term mutagenicity tests, is important for the assessment of human risk. (19 refs)

- 79-6047 DDT and Cancer. (Eng) Jukes, T. H. (Univ. California, Berkeley, CA 94704). *Clin Toxicol* 14(4): 461-463; 1979.

The claim that DDT exposure causes cancer is disputed. DDT feeding in rats for 2 yr (most of the rat lifespan) results in a minimal hepatocarcinogenic tendency. Liver changes identical to those produced by phenobarbital, pyrethrum, and other chemicals were seen 14 wk after DDT feeding in rats and could be produced in rabbits, mice and guinea pigs, but not in chickens, dogs, cats, and monkeys or large domestic animals. In another study, no tumors were found in three generations of dogs (>500 animals) raised on diets containing high DDT doses. Factory workers in DDT production and men who have been involved in spraying DDT for many years have shown no indication of DDT causing cancer. This is in marked contrast to other industrial carcinogens, including asbestos, arsenic, vinyl chloride, and dimethylchloroether. According to the World Health Organization, extensive medical tests of 150 persons with prolonged occupational exposure to large doses of DDT have not revealed any related findings except increased storage and excretion of DDT and its metabolites and mild stimulation of hepatic microsomal enzymes. (no refs)

- 79-6048 Short-Term Tests for Carcinogens and Mutagens. (Eng) Hollstein, M. (Dept. Biochemistry, Univ. California, Berkeley, CA 94720); McCann, J. *Mutat Res* 65(3): 133-226; 1979.

Short-term tests used to determine the potential mutagenicity and carcinogenicity of chemicals are reviewed. The major methods were placed into one of eight general categories: tests in prokaryotic microorganisms, phages, etc.; tests using eukaryotic microorganisms; mutagenesis tests in cultured mammalian cells; tests for DNA-repair effects and DNA-replication inhibition; in vitro transformation tests; in vivo tests in mammals; tests in insects; and in vitro and in vivo mammalian cytogenetics tests. Tests from each of these categories were used to analyze 72 carcinogens and mutagens. Many tests detected chemicals from a wide variety of different chemical classes, some chemicals being potent in one test system and weak in others. Qualitatively, results in one short-term test tended to reinforce results in other tests, and most carcinogens were positive in a number of short-term tests; exceptions included DDT, DDE, dieldrin, phenobarbital, and diethylstilbestrol. Results in the different tests were internally consistent in that each system tended to detect some classes of carcinogens more efficiently than others. The tests tended to complement one another in that carcinogens not detected by some tests were detected by others. The following essential components of a complete evaluation of short-term tests are discussed briefly: the relative effectiveness of short-term tests in identifying chemicals as "noncarcinogenic"; the predictive value of short-term tests; the relationship between potencies in these tests and potency in vivo; designing test batteries; and the role of short-term tests in cancer and genetic hazard policy. (678 refs)

- 79-6049 Risk Assessment of Ethylene Oxide and Other Compounds. (Eng) Ehrenberg, L. (Wallenberg Lab., Stockholm Univ., Stockholm, Sweden). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978*. McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 157-190; 1979.

The principles used for risk assessment of mutagenic and carcinogenic compounds are reviewed using ethylene oxide as a model compound. Quantitative analysis of existing data is needed to determine the resolving power of biological tests, to make quantitative risk assessments for man, and to determine whether a negative test excludes an unacceptable risk. Ionizing radiation is the only environmental factor that has been subjected to quantitative risk estimates. Three generalizations favor the application of the unit of radiation risk as a general unit of chemical risk (ie, establishing the "rad-equivalence" of a unit dose of a chemical): (1) the linearity at low doses of dose-response curves; (2) the finding that mutation frequency is determined by the number of alkylations of certain DNA centers; and (3) the finding that the number of such alkylations per unit amount of DNA that is associated with the same response as 1 rad of gamma radiation is the same in bacteria, plants, and mammals. Risk estimates for animals require knowledge of the in vivo dose associated with the uptake of a certain amount of compound, this dose being determined by the rates of absorption, chemical and metabolic reactions, distribution, transport, and excretion. Measurement of hemoglobin alkylation represents a method for identifying populations at risk and is applicable to primary and secondary mutagens and carcinogens. The same data may be used to quantify the risk using unit radiation risk as a standard. The demonstration of alkylation in vivo can be considered a sufficient criterion of genetic risk, and the demonstration of hemoglobin alkylation is a criterion of risk of heritable damage. (26 refs)

- 79-6050 Chloroprene (2-Chloro-1,3-butadiene)-- What Is the Evidence for Its Carcinogenicity? (Eng) Haley, T. J. (Dept. Health, Education, and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR 72079). *Toxicol Annu* 3: 153-170; 1979.

The chemical, biological, and potentially carcinogenic activities of chloroprene are reviewed. Topics discussed include the synthesis and analysis of chloroprene, its biochemistry and metabolism, its toxicity for animals and humans, and its carcinogenicity. Sc injection of chloroprene into rats before or after transplantation of Crocker's murine sarcoma resulted in an acceleration of tumor growth. Chloroprene and its derivatives induced skin cancers in 137/24,989 Soviet workers. The neoplasms were found most often on the face, neck, nose, and hands, and they were associated with chronic dystrophic or inflammatory skin conditions. Lung cancer was also found in 87/19,979 chloroprene workers, 18 with direct and prolonged exposure to chloroprene and 16 with exposure to chloroprene latexes. (149 refs)

- 79-6051 Colon Cancer Epidemiology and Possible Causation. (Eng) MacLennan, R. (Sch. Public Health and Tropical Medicine, Building A27, Univ. Sydney, Sydney, New South Wales 2006, Australia). *Nutr Cancer* 1(3): 64-66; 1979.

The possible factors responsible for the development of colon cancer are reviewed. Colon cancer is among the most common cancers in most Western countries but occurs in a much lower incidence in most developing countries. Colon cancer rates for males and females are similar, whereas rectal cancer rates show variations with sex. Japanese migrants in Hawaii show rapid increases in colon cancer incidence within 20-30 yr of migration with shifts toward the American pattern. In general, populations in transition show increases in the diseases. Social class is also a risk factor, the incidence increasing with income. The distribution patterns for

colon cancer are consistent with the theory that diet is involved in its etiology. High correlations have been shown between colon cancer and meat and total fat consumption. There is indirect evidence for a negative association with dietary fiber. It has been suggested that bile acids are metabolized by intestinal bacteria to carcinogens or cocarcinogens that act on the colon and rectum. A high correlation was found between colon cancer mortality and the intestinal concentration of dihydroxycholesterol, a bacterial metabolite of bile acids. A recent study of colon cancer incidences in Scandinavia and New York suggested that colon cancer probably has a multifactorial etiology. (17 refs)

- 79-6052 Asbestos and Smoking (Letter to Editor). (Eng) Selikoff, I. J. (Mount Sinai Sch. Medicine, City Univ. New York, New York, NY); Hammond, E. C. *JAMA* 242(5): 458-459; 1979.

The association between smoking, asbestos, and cancer is reviewed. The two most common asbestos-induced cancers are lung cancer and mesothelioma. The former is usually related to cigarette smoking, whereas the latter is not. Similarly, cancers of the esophagus, larynx, and oropharynx occur in excess primarily in asbestos workers who have a history of cigarette smoking, whereas the incidences of colorectal and renal cancers are increased in such workers regardless of smoking history. While asbestos by itself somewhat increases the risk of cancer, smoking by itself causes a major increase. One in every five deaths among asbestos workers is due to lung cancer. Smoking, which causes bronchitis, emphysema, and fibrosis, adds an undesirable and sometimes insupportable burden to asbestos-induced pneumoconiosis. All workers known to have been exposed to asbestos should be advised never to smoke or to stop smoking as soon as possible. Periodic medical surveillance would further reduce the risk of gastrointestinal, oropharyngeal, laryngeal, and renal cancers, and therapy for superimposed pulmonary infections would limit the incidence of asbestosis. (4 refs)

- 79-6053 Occupational Lung Cancer and Smoking: A Review in the Light of Current Theories of Carcinogenesis. (Eng) Chovil, A. C. (Industrial Medicine Consultant, Ontario Workmen's Compensation Board, 2 Bloor St. E., Toronto, Ontario M4W 3C3, Canada). *Can Med Assoc J* 121(5): 548-550, 553-555; 1979.

Modern theories of carcinogenesis are considered as they apply to the induction of lung cancer by tobacco smoking and occupational exposure to carcinogens. Some of the known and postulated factors affecting carcinogenesis are discussed, with particular reference to cocarcinogenesis and thresholds. Factors affecting the intensity of smoking exposure are reviewed; and the generally accepted occupational lung carcinogens are listed, including asbestos, arsenic, nickel, chromates, chloromethyl ethers, coal tar distillates, mustard gas, and ionizing radiation. Relative risks for the various carcinogens according to smoking status (where known) are presented. The carcinogens are considered individually, and known or postulated interactions with smoking are discussed. (54 refs)

- 79-6054 Carcinogenic Actions of Inorganic Constituents of Particulates Suspended in Air. (Ger) Brockhaus, A. (No affiliation given). *Lufthyg Silikoseforsch* 11: 99-106; 1978.

In order to evaluate the carcinogenic importance of various contaminants suspended in air, the evidence for carcinogenicity of several inorganic elements and compounds is reviewed. Results summarized by the International Agency for Research on Cancer indicate that, in addition to asbestos, nickel compounds, nickel-carbonyl, insoluble chromium compounds, and beryllium and Be compounds are also carcinogenic air pollutants. Five epidemiological studies show that the carcinogenic actions of asbestos and cigarette smoke are synergistic. There is also evidence that synergism exists between exposure to Ni compounds found in refineries and smoking. Although higher than expected cancer rates have been found in iron miners, the substances responsible have not been identified. A study of lung cancer incidence from 1950 to 1969 in the US revealed an above av incidence ($p < 0.05$) in 36 areas in which mining and refining of heavy metals, especially Cu, Pb, and Zn was done. Tobacco use was not investigated in this study. The results of these studies may suggest that suspected carcinogenic air pollutants interact and may act synergistically; for this reason, future epidemiological and animal studies should concentrate on the effects of various combinations of air pollutants. (20 refs)

- 79-6055 Carcinogenic Properties of Vulvovaginal Preparations (Letter to Editor). (Eng) Venter, P. F. (Dept. Obstetrics and Gynecology, Univ. Orange Free State, Bloemfontein, South Africa). *S Afr Med J* 56(16): 625; 1979.

The possible carcinogenic properties of vulvovaginal preparations are discussed. Some chemicals used in vaginal preparations that have been implicated in carcinogenesis are arsenic, 8-hydroxyquinoline, nitrofur, ichthammol, sulfonamides, metronidazole, certain spermicides, talc, asbestos, and gentian violet. The possible formation of carcinogenic nitrosamines; the possibility that chemical substances deposited in the vagina could migrate to the peritoneal cavity; and the fact that the uterus, fallopian tubes, ovaries, and peritoneal cavity are in direct contact with substances that may be present in the more external genital structures should be considered. (4 refs)

- 79-6056 Novel Activation Mechanism for the Promutagenic Herbicide Diallyl. (Eng) Schuphan, I. (Pesticide Chemistry and Toxicology Lab., Dept. Entomological Sciences, Univ. California, Berkeley, CA 94720); Rosen, J. D.; Casida, J. E. *Science* 205(4410): 1013-1015; 1979.

Diallyl (S-2,3-dichloroallyl diisopropylthiocarbamate) and triallyl sulfoxide were prepared and their degradation chemistry examined. *cis*-Diallyl sulfoxide underwent a rapid and quantitative conversion to 2-chloroacrolein and the carbamoylsulfonyl chloride. The *trans* isomer gave the same compounds but more slowly. Triallyl sulfoxide degraded to 2-chloroacrylyl chloride. The products originate from a [2,3] sigmatropic rearrangement to a S-O-allylsulfenyl ester followed immediately by a 1,2-elimination reaction. Liver microsomes extensively metabolized the diallyl isomers but only in the presence of NADPH. Rats given carbonyl- ^{14}C -labeled diallyl po expired 20% $^{14}\text{CO}_2$ and their urine contained 62% mercapturic acid conjugate and 9% other metabolites originating from the carbamoyl-glutathione (GSH) derivative. Dichloroallylsulfonic acid was the major metabolite of (allyl- ^{14}C)diallyl in mice and rats and their microsomal-NADPH systems. These results indicate that under biological conditions, diallyl sulfoxide undergoes either the major detoxifying GSH conjugation or the minor, competing [2,3] sigmatropic rearrange-

ment reaction followed by 1,2-elimination to liberate a toxicologically significant metabolite, most probably 2-chloroacrolein. Triallate sulfoxide is unstable and is probably the proximate mutagen. (14 refs)

- 79-6057 Formation of Carcinogenic N-Nitroso Compounds in the Living Organisms and in the Environment. (Hun) Borzsonyi, M. (Országos Kozegeszsegügyi Intezet, Budapest, Hungary); Pinter, A. *Magy Onkol* 23(3): 171-179; 1979.

Studies on the formation of carcinogenic N-nitroso compounds in vivo and in the environment are reviewed. The formation of N-nitroso compounds from precursors is enhanced by certain bacteria, eg, *Staphylococcus aureus*, by thiocyanate present in human saliva; by SO_4 , Cl, Br, I, and PO_4 ions; and by complexes of Mo, Fe, Cu, Hg, and Co. The most important precursors of N-nitroso compounds include ephedrin, ethambutol, folic acid, morpholine, phemetrazine, piperazine adipate, dulcin, aminopyrine, Analgin, chlorpromazine, dextropropoxyphene, oxytetracycline, pyribenzamine, quinacrine, disulfiram, nicotine, nornicotine, hydroxypyrrolidine, proline, pyrrolidine, methylguanine, agmatin, trimethylaminoxide, trimethylamine, sarcosine, spermidine, spermine, as well as the active ingredients of some pesticides, such as carbaryl, propoxur, Hopcide, Baygon, Carbofuran, Benlate, Carbendazim, Dodin, benzthiazurone, Fenuron, Ferbam, Thiram, Ziram, semicarbazide, Alar, atrazine, simazine, and Triforin. The carcinogenic substances formed by the nitrosation include N-ephedrin, N-ethambutol, N-folic acid, N-morpholine, N-phenmetrazine, dinitrosopiperazine, dimethylnitrosamine, nitrosoanabasine, nitrosohydroxypyrrolidine, nitrosoproline, nitrosopyrrolidine, N-nitrososarcosine, 3-butenyl derivatives, N-nitrosocarbaryl, N-nitrosopropoxur, N-nitrosocarbofuran, methylnitrosourea, diethylnitrosamine, N-nitrosotriazine, and 1,4-dinitrosopiperazine. (71 refs)

- 79-6058 Problems of Dose-Response Studies in Chemical Carcinogenesis with Special Reference to N-Nitroso Compounds. (Eng) Schmahl, D. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Heidelberg, W. Germany). *CRC Crit Rev Toxicol* 6(3): 257-281; 1979.

The benefits and limits of dose-response experiments in chemical carcinogenesis are reviewed. Dose-response experiments can give information concerning the potency of a carcinogen, its mode of action, its threshold (risk assessment), and its effect in combination experiments if they are performed with an appropriate experimental design. Variables which must be considered in the design of dose-response experiments include the animal species and strain, dose range, mode and frequency of application, and length of observation period. Extrapolations of experimental results to other strains or species can only be made speculatively and with reservations. In estimating the carcinogenicity of N-nitroso compounds for man from data obtained in animal experiments, relatively firm conclusions can be drawn because the compounds have been tested in a variety of animal species and have proved to be more or less equally carcinogenic. This applies to both the dose which is required for tumor induction and the organotropism of the effect. The N-nitroso compounds can cause malignant tumors in practically all parenchymatous organs after systemic application, except in the ovaries, testicles, uterus, and adrenal gland. Repeated single applications of carcinogen are more effective than one application of a high dose. The effect obtained with one partial dose is irreversible and remains capable of

summation. It is concluded that the greatest practical importance of dose-response studies is the determination of tolerance limits for environmental chemicals. (103 refs)

- 79-6059 Biological N-Methylation and Demethylation and Pathological Cell Proliferation. (Hun) Tyihak, E. (Gyogynoveny Kutato Intezet, Budakalasz, Hungary). *Magy Kem Lapja* 34(4/5): 190-198; 1979.

Recent studies on possible relationships between biological N-methylation, N-demethylation, and malignant cell proliferation are reviewed. There is an evident correlation between hypermethylation in the human body and malignant cell proliferation. The hypermethylation may be a consequence of increased enzymatic transmethylation or spontaneous chemical methylation. In the latter reaction formaldehyde is the foremost agent suspected of being formed either from nitrosamines or as a result of increased demethylase activity in the presence of aromatic hydrocarbons or viruses in different tissues. Increased levels of methylated nucleic bases have been found in the urine of cancer patients compared with healthy controls. Ne, Ne, Ne -trimethyl-L-lysine has been found to have a considerable tumor growth-enhancing effect in mice with NK/LY ascitic tumors; the number of tumor cells and the percentage of the cells in mitosis were increased after administration of single or multiple 5-10 mg/kg doses. (61 refs)

- 79-6060 Are Nitrites and Sweeteners Carcinogenic? (Swe) Werko, L. (Astra AB, Sweden). *Lakartidningen* 76(30/31): 2607-2608; 1979.

The debates and controversies around saccharin and nitrite as food additives in the US are discussed. Saccharin was found to be carcinogenic when administered to laboratory animals in very high doses, and nitrites have a tumor promoting rather than a carcinogenic effect. (5 refs)

- 79-6061 Comparison of Studies on Saccharin and Sodium Nitrite. (Eng) Taylor, J. M. (Div. Toxicology, Food and Drug Admin., Washington, DC 20204); Morgenroth, V. H. *J Assoc Off Anal Chem* 62(4): 883-888; 1979.

A review of long-term animal studies of saccharin and sodium nitrite was undertaken to assess the effect of variations in selected elements of protocol on the results obtained. These elements were divided into four general categories: design, including selection of test animals, basal diet, dosage form and doses of test substance, route of administration, and duration of exposure; observations, including gross observations during life and at necropsy, clinical tests, and histopathology; performance, including conduct of the test and animal husbandry; and analytical procedures, including chemical and statistical methods. Because many of these elements were not fully discussed in the study reports, it was often impossible to determine what actually had been done. The review of various saccharin studies suggested that bladder tumors resulted following in utero exposure, whereas in utero exposure to sodium nitrite did not appear to cause reticuloendothelial changes. The numerous variations in protocol in the nitrite studies precluded identification of a prime element responsible for the variations in reticuloendothelial changes observed. It can be concluded that achievement of reproducibility in long-term studies requires minimal variations in protocol for new studies. (11 refs)

REVIEW

- 79-6062 Carcinogenicity of Cosmetic Materials. (Eng) Prunieras, M. (Lab. Human Skin Tumors [INSERM FRA 14], Fondation Adolphe de Rothschild, 29 rue Manin, 75019 Paris, France). *Adv Pharmacol Ther* 9: 277-287; 1979.

The carcinogenicity of cosmetic materials is reviewed. Preliminary data have indicated that at least nine ingredients used in the dyes are carcinogenic when fed to rats and mice, and two semipermanent hair dyes have been shown to be carcinogenic for mice following topical application. Various regulations exist concerning the amounts of carcinogenic polycyclic hydrocarbons which may be incorporated into mineral oils, which are used in large quantities in cosmetics. Skin care products, cosmetics, beauty aids, and hair shampoos also may contain variable amounts of N-nitrosodiethanolamine, a compound which was proven carcinogenic in rats. A wide variety of materials commonly used in cosmetic creams, milks, and other products have been shown to induce acanthosis in guinea pig skin; these include paraffin oil, petrolatum jelly, castor oil, lauric and oleic acids, and fatty acids. A basis for dealing with known or suspected occupational carcinogens has been provided by the American Occupational Safety and Health Administration, but clearance of cosmetic products by public health services prior to marketing is not mandatory in any country. It is important to understand that if some cosmetic material includes chemical ingredients with carcinogenic potential, this potential is very weak. (33 refs)

- 79-6063 Factors Influencing DNA Damage and Its Repair with Cellular Implications for Toxicology. (Eng) Sarma, D. S. (Dept. Pathology, Univ. Toronto, Medical Sciences Bldg., Ontario M5S 1A8, Canada); Rajalakshmi, S.; Udupa, R. S.; Farber, E.; Rao, P. M. *Adv Pharmacol Ther* 9: 71-79; 1979.

Factors influencing DNA damage and repair are reviewed, and the cellular implications for toxicology are discussed. Carcinogens can, either directly or after suitable metabolic activation, interact with both the purines and pyrimidines in DNA and, in some cases, with the phosphate as well. In addition to the pure chemical factors that influence the sites of interaction of carcinogens with DNA, the availability of these sites in chromatin DNA is determined by the several hierarchies of organization of the DNA in chromatin. Carcinogens exhibit preferential interactions with some regions of the DNA (eg, dimethylnitrosamine methylates predominantly the DNase I-digestible regions of chromatin DNA). The availability of the DNA in chromatin to repair enzymes is also subject to restrictions imposed by the hierarchy of the folding of DNA in the nucleus. Although the precise role of cell proliferation in cellular damage is not fully understood, the available data are compatible with the hypothesis that the replication of DNA with unrepaired damage helps fix the damage in the daughter strand, a step that may be obligatory in the toxicologic, mutagenic, and carcinogenic processes in the cell. (45 refs)

- 79-6064 New Aspects of Nitrosamine-induced Carcinogenesis. (Eng) Magee, P. N. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140). *Adv Pharmacol Ther* 9: 81-91; 1979.

The metabolism and organ specificity of the N-nitroso compounds are reviewed. Nitrosamines and other N-nitroso compounds are effective carcinogens, inducing tumors in most organs in a wide range of species. These compounds are also powerfully mutagenic, and several have been shown to alkylate DNA and other cellular

macromolecules in different organs. In the case of dimethylnitrosamine, the metabolic pathway leading to the alkylating intermediate is quantitatively the major one. The organ specificity or organotropism of the N-nitroso compounds may be dependent on the capacity of the organs to activate them, when necessary, and on the variable persistence of certain alkylated components of DNA. Other, as yet unidentified, factors are probably also involved. (74 refs)

- 79-6065 The Role of DNA Alkylation and Repair in the Toxic and Carcinogenic Effects of Alkyl Nitrosoureas. (Eng) Kleihues, P. (Pathologisches Institut der Universität Freiburg, Freiburg, W. Germany). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 191-205; 1978.

The formation of DNA lesions and their persistence in various organs in vivo are reviewed. Monofunctional alkylating carcinogens react at all available nucleophilic sites in DNA bases. Compounds that react predominantly at nitrogen atoms in DNA bases are generally weak carcinogens, whereas agents which lead preferentially to O-alkylation are usually strong carcinogens. Some alkylated bases are removed from DNA by chemical depurination, others by enzymatic excision, and some by both mechanisms. The loss of alkylated bases leads to the formation of apurinic sites that contribute to the cytostatic and lethal effects of alkylating agents. In rats, the location of neural and renal neoplasms seems to be related to a deficiency of the target tissues in excising O⁶-alkylguanine from their DNA. This correlation is less consistent in mice; additional genetically determined factors may modify tumor development following promutagenic changes in DNA. The excision repair system for O⁶-methylguanine in rat liver can be inhibited in a dose-dependent manner with sublethal doses of methyl nitrosourea and related carcinogens. A similar dose-dependent inhibition of the rate of excision does not seem to exist in the brain. It is concluded that the data on the interaction of neuro-oncogenic agents with DNA support the hypothesis that the induction of tumors is initiated by a change in gene structure rather than in gene function. (55 refs)

- 79-6066 Critical Review of the Toxicology of Coumarin with Special Reference to Interspecies Differences in Metabolism and Hepatotoxic Response and Their Significance to Man. (Eng) Cohen, A. J. (Toxicology Advisory Services, 25, Cedar Road, Sutton, Surrey, England). *Food Cosmet Toxicol* 17(3): 277-289; 1979.

The validity of studies indicating that rats fed coumarin at 5,000 or 6,000 ppm for 2 yr develop bile duct carcinomas has been questioned, in view of the absence of significant metastasis and of negative findings in an earlier carcinogenicity study. Coumarin does not act as a cocarcinogen in mouse skin and was not found to be carcinogenic following sc administration in rats in a limited study. Rats metabolize coumarin differently than do humans, which makes the use of this species for predicting the hepatotoxic risk in humans questionable. Because metabolism appears to be an important factor in determining the hepatotoxic response, species differences should be considered when evaluating the hepatotoxic hazard to humans. (58 refs)

- 79-6067 DNA Repair. (Eng) Setlow, R. (Biology Dept., Brookhaven Natl. Lab., Brookhaven, NY). In: *Bran-*

bury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978. McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 81-95; 1979.

DNA repair in bacterial and mammalian systems is reviewed. Excision repair has been categorized into two types: long patch, in which a region of DNA on the order of 100 nucleotides is removed and replaced; and short patch, which involves replacement of 1-10 nucleotides. The former is caused by UV and other bulky types of damage, and the latter occurs in cells exposed to x-rays or some alkylating agents. A third type of excision repair, zero patch, involves the replacement of zero nucleotides and has been documented for the 0-6 alkyl guanine following alkylation damage. Individuals with xeroderma pigmentosum (XP) are deficient in DNA repair; their cells are highly subject to mutation in culture; and they show a high incidence of skin cancer, especially malignant melanoma. XP cells in culture are sensitive to UV and many other agents. Individuals with ataxia telangiectasia (AT) show a fivefold increased cancer risk compared with the general population and are approx five times more sensitive to x-rays; their cells are sensitive to x-rays and alkylating agents in culture. The molecular nature of the defect in AT is unknown. Individuals with Fanconi's anemia, which involves a deficiency in the repair of cross-links, are also at increased risk of cancer, particularly leukemia. These data are discussed by a panel. (22 refs)

79-6068 Estimating Radiation-induced Genetic Disease Burdens. (Eng) Abrahamson, S. (Dept. Zoology, Univ. Wisconsin, Madison, WI). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978.* McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 147-156; 1979.

The methodology employed by the BEIR committee in developing risk estimates for the genetic effects of radiation is reviewed. The committee employed a relative-mutation-risk procedure using a value that is the inverse of the amount of radiation required to double the current incidence of mutationally maintained disease in a continuously exposed population. The methodology is discussed by a panel. (4 refs)

79-6069 Genetic Damage from Diagnostic Radiation? A Critique of the Bross and Natarajan Study. (Eng) Oppenheim, B. E. (Dept. Radiology, Indiana Univ. Sch. Medicine, 1100 W. Michigan St., Indianapolis, IN 46223). *JAMA* 242(13): 1390-1393; 1979.

A critique of a previous analysis of the effect of intrauterine exposure to diagnostic radiation is presented. In the original article, it was hypothesized that low-dose fetal irradiation in the 0.5-5.0 rad range confines its damage to 1% of exposed subjects and that for this affected group there is a 5,000% increase in the risk of leukemia compared with that in unexposed subjects. According to the present author, the radiation doses are grossly misrepresented. At most one-third of the irradiated subjects in the previous study were exposed directly to the x-ray beam (giving an exposure in the 1-rad range), as occurs when the mother receives an abdominal x-ray; the remaining subjects were exposed to a dose of about 0.001

rad, as their mothers received only a chest x-ray. In the original article, the proportion of subjects aged 1 to 4 whose mothers received x-rays during pregnancy was reported to be 0.289. This value is appropriate for the exposed fraction of nonleukemic subjects, but a value of 0.379 should have been used for the exposed fraction of leukemic subjects. Inappropriate sampling techniques were used to select members of the unexposed group because children with postnatal x-rays were excluded from the unexposed group. It is concluded that the original article produced no evidence that the radiation hazard is any greater than that indicated by previous investigators. (18 refs)

79-6070 Radiation-induced Cancer. (Eng) Baum, J. W. (Safety and Environmental Protection Div., Brookhaven Natl. Lab., Upton, NY 11973). In: *Branbury Report. 1. Assessing Chemical Mutagens: The Risk to Humans. Proceedings of a Meeting sponsored by the Office of Toxic Substances, U. S. Environmental Protection Agency, held in Lloyd Harbor, NY, May 1978.* McElheny, V. K.; Abrahamson, S., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): 367 pp.; 117-134; 1979.

Animal and human data on radiation carcinogenesis and mathematical models that may relate to mutagenesis and carcinogenesis are reviewed. Tissues that are relatively resistant to radiation-induced cancer tend to show sigmoid dose-effect relations, and the more densely ionizing radiations (eg, alpha particles) are usually more effective than x- or gamma-rays in inducing tumors. More sensitive tissues may respond at even very low doses, and the slope of the dose-response curve at low doses may be nearly linear. The effect of chronic exposure to x- or gamma-rays is often less than that of acute exposure. The thyroid is a moderately sensitive organ; the dose response for it may be linear at very low doses after which it peaks and then comes down. Mammary tumors are seen very early in irradiated rats, and when the dose is higher the incidence increases. Thus, both promotion and induction occur. A model is proposed in which carcinogenic events are assumed to occur naturally at a constant rate and that there are six different classes of cells that appear progressively as the events occur. The results of one experiment suggested that radiation-induced steps occur two at a time. Population heterogeneity in human epidemiological studies can drive dose-response curves toward a power function less than the inherent underlying power functions of the various subpopulations. For all malignancies among survivors of the Hiroshima bombing and for Japanese women with breast cancer, the dose response was about a one-half power function in early analyses, but, according to the multiple-event model, it would be expected to be linear when the populations have completed their life spans. Children in human studies have proven to be slightly more sensitive than adults. Radiation protection standards must consider the risk vs the cost of reducing that risk. (18 refs)

79-6071 Skin Cancer After PUVA Treatment for Psoriasis (3 Letters to Editor). (Eng) Morgan, R. W. (Univ. Toronto, Toronto, Ontario M5S 1A8, Canada); Spellman, C. W.; Stern, R. S.; Thibodeau, L. A.; Parrish, J. A.; Fitzpatrick, T. B. *N Engl J Med* 301(10): 554-555; 1979.

Three letters concerning an article on skin cancer following PUVA (methoxypsoralen plus A-range UV light) treatment for psoriasis are presented. The results of studies in mice with topical 8-methoxypsoralen (8-MOP) and subcarcinogenic levels of B-range UV light suggest that failure to reject a transplanted tumor and

development of a tumor in a treated host may result from previous induction of specific suppressor cells. These phenomena may also occur in patients treated with PUVA. The absence of an adequate control group is discussed in two letters. The authors of the original article contend that valid observations can be made that suggest an increased risk of cutaneous carcinoma in a subset of patients treated with PUVA, even in the absence of a rigorous control group. (8 refs)

- 79-6072 Cancer and Slow Virus Diseases--Some Common Features. (Eng) Gross, L. (Veterans Admin. Medical Center, Bronx, NY 10468). *N Engl J Med* 301(8): 432-434; 1979.

Some features common to cancer and slow virus diseases are reviewed. Most malignant tumors, leukemias, and lymphomas in animals are caused by transmissible oncogenic viruses, and it is reasonable to assume that neoplastic diseases in man can also be caused by viruses. Several chronic degenerative diseases of the CNS are caused by transmissible viruslike agents: presenile dementia, scrapie (in sheep), and kuru. The diseases appear after very long latency periods and frequently last for several years or even decades. They are slow, progressive, and always fatal. Pathologic changes are essentially limited to the brain and are characterized by widespread vacuolar neuronal, spongiform degeneration and gliosis of the gray matter. Presenile dementia can be transmitted through corneal transplantation, brain surgery, or ingestion of contaminated food. The scrapie, kuru, and presenile dementia viruses readily cross species following experimental inoculation. Although oncogenic viruses are different from the viruslike agents that cause slow virus diseases, both groups of viruses are usually transmitted from one generation to another, and both groups have the ability to evade the immunologic responses in their hosts. (13 refs)

- 79-6073 The Scientific Heritage of Professor Zilber and his Contribution to Virus-Genetic Theory of Malignant Tumors. (Eng) Shevlyaghin, V. Y. (N. F. Gamaleya Inst. Epidemiology and Microbiology, AMS USSR, Moscow, USSR). *Neoplasma* 26(2): 113-123; 1979.

The scientific heritage of Professor Zilber, who first proposed the virus-genetic theory of malignant tumors, and his contribution to this theory are reviewed. Zilber's original hypothesis was that the etiological factor in tumors induced by physical and chemical agents is a tumor virus. Zilber's theory that the tumor virus is integrated into the genome of the cell was confirmed after Zilber's death. (131 refs)

- 79-6074 Inheritance and Expression of Chicken Genes That Are Related to Avian Leukosis Sarcoma Virus Genes. (Eng) Robinson, H. L. (Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545). *Curr Top Microbiol Immunol* 83: 1-36; 1978.

The inheritance and expression of chicken genes that code for avian leukosis sarcoma virus (ALSV) or viral products are reviewed. Topics covered include phenotypes for the expression of endogenous ALSV, expression of endogenous viral genes, inheritance of endogenous ALSV expression, and the immune response of chickens to endogenous viral antigens. No direct relationship between the expression of endogenous ALSV and the oc-

currence of cancer has been observed in chickens. Some viruses that cause neoplasia in chickens contain genes closely related to those of an endogenous ALSV, RAV-0. Some of these oncogenic ALSVs have additional genes not found in RAV-0, eg, sarcoma, myeloblastosis, erythroblastosis, myelocytomatosis, and carcinoma viruses. It is possible that the oncogenic Rous sarcoma virus (RSV) may have arisen from the recombination of RAV-0 or RAV-0-like viruses with *sarc*, a highly conserved cellular gene present in the microchromosomes of chicken cells. Other oncogenic ALSVs contain only those genes found in RAV-0 but have *env* genes that have diverged from RAV-0, these viruses cause leukosis, a disease that results in the appearance of metastatic B cells in the liver and spleen. It is speculated that the envelope antigens of the RAV-0 virus may not initiate the same immune response as the envelope antigens of oncogenic ALSV. It is also possible that the envelope antigens of the oncogenic viruses alter normal host controls over B cell growth so that metastatic disease appears. (186 refs)

- 79-6075 Permanent Teratocarcinoma-derived Cell Lines Stabilized by SV40 Transformation. (Eng) Levine, A. J. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ 08540). In: *Oncodevelopmental Antigens*. Fishman, W. H., Busch, H., eds. (New York: Academic Press): Methods in Cancer Research Vol. 18, 409 pp.; 333-357; 1979.

The literature on permanent teratocarcinoma-derived cell lines stabilized by simian virus 40 (SV40) transformation is reviewed. SV40 infection is clearly required for establishment of the teratoma-derived cell lines (SVTER), and all the SVTER cell lines are only minimal transformants with respect to their growth potential in culture. The teratocarcinoma-derived cells appear to exert a strong influence over the SV40 genome and tumor antigen, so that these cells and cell lines retain a more normal phenotype in vitro and in vivo. The growth properties of embryonal carcinoma cells resembled those of fully transformed and tumorigenic SV40-transformed cell lines. The SVTER lines contained a number of other properties demonstrating that they are differentiated from embryonal carcinoma cells, and the teratocarcinoma-derived cells have distinct patterns of differentiation and sets of gene expression. It is possible, however, that the SVTER cell lines represent aberrant examples of developmental pathways. (68 refs)

- 79-6076 Viral Origin of Antigenic Markers in Simian Papovavirus SV40 Transformed Cells. (Eng) Tevethia, S. S. (Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Greenfield, R.; Pretell, J.; Tevethia, M. J. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, E. W., ed. (New York: Elsevier): 590 pp.; 67-72; 1978.

The early region of simian papovavirus 40 (SV40) DNA codes for two proteins: a 90,000- to 100,000-dalton (90K-100K) protein and a 17K protein. Both of these early gene products are precipitated by sera from animals bearing SV40-induced tumors [anti-tumor (anti-T) sera] and are therefore designated as T antigens. The same region also specifies transplantation-rejection antigen (TrAg) at the surface of SV40-infected or SV40-transformed cells and is involved in tumor rejection. Genetic and immunological evidence suggests that the antigenic sites for T and TrAg may be located on the same protein but that they are distinct. (25 refs)

- 79-6077 The Moloney Leukemia Virus-determined Cell Surface Antigen: Separation from Cell Membrane-associated Virion Proteins. (Eng) Fenyo, E. M. (Dept. Tumor Biology, Karolinska Inst., Stockholm, Sweden). In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, E. W., ed. (New York; Elsevier): 590 pp.; 47-51; 1978.

Current knowledge concerning a cell-surface antigen associated with Moloney murine leukemia virus (M-MuLV) infection of mouse cells is reviewed. The M-MuLV-determined cell-surface antigen has been separated from H-2 and virion proteins associated with the cell membrane by Sephadex G-200 chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Multiple mol wt species possessing antigenic determinants for Moloney cell-surface antigen (MCSA) have been detected. Antibody-induced capping of gp71 and p15E did not affect the cell-surface distribution of MCSA, indicating that MCSA is a distinct entity. In contrast, MCSA cocapped with p30 and p12 virion protein antigens. This suggests that MCSA is linked to *gag* proteins on the lymphoma cell surface. (19 refs)

- 79-6078 The Role of Viral Transformation and Cytogenetic Changes in Viral Oncogenesis. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden). *Ciba Found Symp* (66): 335-358; 1979.

The interaction of Epstein-Barr virus (EBV) with the human B lymphocyte, particularly as it relates to Burkitt's lymphoma (BL), is reviewed. In vitro EBV-transformed lymphoblastoid cell lines are initially purely diploid, do not grow in nude mice, and do not plate in agarose. BL biopsies and derived lines are not purely diploid, are regularly tumorigenic in nude mice, and grow in agarose. This implies that in vitro immortalization cannot be equated with in vivo tumorigenicity. For malignant growth in vivo, additional changes at the cytogenetic level appear to be required. Ninety-seven percent of the African BL examined are EBV-DNA- and EB nuclear antigen (EBNA)-positive. Only 22% of non-African BL cases carry the viral genome. About 90% of in vivo BL tumors studied were found to contain the same 14q+ marker. This marker has also been found in EBV-negative BL. Studies of the pathogenesis of BL suggest that it proceeds in three steps: (1) primary EBV infection in a young child, which immortalizes some B lymphocytes in vivo; (2) chronic stimulation of the proliferation of EBV-carrying preneoplastic cells by an environmental promoting agent (possibly malaria); and (3) chance appearance of chromosomally abnormal variants in the stimulated tissue; after certain types of chromosomal changes, particularly those leading to the 14q+ marker, the affected B lymphocyte no longer responds to negative feedback and proliferates. X-ray-, dimethylbenzanthracene-, and virus-induced experimental murine T lymphomas all show the same chromosomal change: trisomy 15. The fact that the same chromosomal anomaly is found in the ultimate tumor regardless of the initiating agent, suggests that the cytogenetic change, rather than the viral transformation, is the essential factor in oncogenesis. (22 refs)

- 79-6079 Tumor-associated Viruses of the Syrian Hamster: Relation to Neoplasia. (Eng) McCormick, K. J. (St. Joseph Hosp. Cancer Res., Stehlin Foundation Cancer Res., Houston, TX 77002); Trentin, J. J. *Prog Exp Tumor Res* 23: 13-55; 1979.

The tumor-associated indigenous hamster viruses and their possible role in neoplastic growth in this species are reviewed. The discussion is limited to the hamster papovavirus, the R-type particle, the intracytoplasmic A-type particle, and the C-type virion. The evidence indicates that the papovavirus and certain C-type virions are infectious and that, in the case of certain tumors, they are related to the neoplastic processes of the host. However, the importance of the type R and intracytoplasmic A-type virus like particles (VLP) in the induction of tumors in the hamster is not clear. Although activation or enhancement of certain viruses or VLP appears to occur through alterations in cellular metabolism via chemical or viral treatments, the mechanisms of activation and the probable concomitant interactions with the immune system of the host are completely unknown. (191 refs)

- 79-6080 The Hepatitis B Virus and Its DNA Polymerase: The Prototype Three-D Virus. (Eng) Hirschman, S. Z. (Div. Infectious Diseases, Mount Sinai Sch. Medicine, New York, NY 10029). *Mol Cell Biochem* 26(1): 47-67; 1979.

Studies concerning hepatitis B virus (HBV) are reviewed. The present concept of HBV is that of a small DNA-containing virus comprised of a 27-nm core with an outer coat of protein to produce a complete virion with a diameter of 42 nm. The core contains circular DNA comprised of 60% double-stranded and 40% single-stranded DNA. The core also contains a unique DNA-dependent DNA polymerase, which fills in the single-stranded gaps that may be in any part of the one strand of the DNA molecule facing the 3'-end of that strand. The surface protein of HBV, hepatitis B surface antigen (HBsAg), contains both lipid ($\leq 30\%$) and carbohydrate (3.6%-6.5%). HBsAg is often detected in particulate form in the blood of infected patients. Several serological techniques have been used, but radioimmunoassay is the most sensitive. There are four major primary subtypes of HBsAg; these appear to be coded by HBV and show different geographic distributions. Hepatitis B core antigen (HBcAg) is detected in the nuclei of infected human hepatocytes and appears to be of simpler chemical composition than HBsAg. In areas where HBV is highly endemic and infection is contracted at a very early age, there appears to be a relationship between HBV infection, cirrhosis, and primary hepatocellular carcinoma. HBsAg is variably found in the tumor cells that have been examined. A virus similar to human HBV has been found recently in woodchucks. (200 refs)

- 79-6081 Embryonic and Fetal Determinants on Virally and Chemically Induced Tumors. (Eng) Coggin, J. H. (Dept. Microbiology and Immunology, Coll. Medicine, Univ. South Alabama, Mobile, AL 36688); Ambrose, K. R. In: *Oncodevelopmental Antigens*. Fishman, W. H., Busch, H., eds. (New York: Academic Press): Methods in Cancer Research Vol. 18, 409 pp.; 371-389; 1979.

The literature concerning tumor-associated cell surface antigens; membrane, tumor-specific, or tumor-associated transplantation antigens; and intracellular antigens located in the nucleus (T antigens) is reviewed with respect to their detection, their role in the primary oncogenic event, and their roles in tumor elimination or progression as they interact with the immune system of the host. Cytostatic immunoglobulin was found in hamsters prior to the frank appearance of sarcoma as a palpable mass and in animals specifically rendered immune to simian virus 40 (SV40) tumor by immunization with irradiated cells or following successful surgical excision. A similar immunoglobulin appeared transiently in the

serum or peritoneal fluid of hamsters during normal pregnancies. Immunity generated by immunization with irradiated fetal cells was effective in preventing SV40 tumor production following live tumor cell challenge and conferred immunity to adenovirus-induced hamster tumors and polyoma-induced hamster tumor cell challenge. Irradiated fetal cells could be used as an immunogen to prevent the induction of primary tumors in hamsters infected at birth with SV40 or adenovirus 31. Consistent transplantation immunity was not detected when the embryo tissues were not irradiated prior to injection. However, irradiation did not appear to activate transplantation antigens. Fetal preparations from multiparous females were generally ineffective as immunogens, and the fetal antigen that could be detected on 9- to 10-day fetuses was not detectable on 11- to 15-day fetuses. The antigenic determinant on hamster fetus was also expressed on mouse and human embryos during the midgestation period. Every major viral or chemically induced tumor system of the rat, mouse, hamster, and guinea pig contains fetal antigens that can produce tumor transplantation resistance when irradiated midgestation fetuses from primiparous donors are used as an immunogen. A clear cross-protection was observed between animals immunized with irradiated SV40 tumor cells and challenged with adenovirus tumor cells and vice versa. (13 refs)

79-6082 Genetic Regulation of Immune Response to TNP-modified Cells. (Eng) Shearer, G. M. (Immunology Branch, NCI, Bethesda, MD 20014); Schmitt-Verhulst, A. M.; Pettinelli, C. B.; Shaw, S. *Gann Monogr Cancer Res* 23: 213-221; 1979.

Parameters characteristic of T-cell-mediated cytotoxic responses against trinitrophenyl (TNP)-modified murine and human cells generated in vitro are reviewed. The specificity of the effector cells generated in such cytotoxic responses is such that optimal lysis is detected when the responding, stimulating, and target cells share H-2K and/or H-2D haplotypes; the stimulating and target cells must both be modified by the same agent. Multiple, H-2-linked immune response genes control the level of cytotoxicity generated against TNP in association with H-2D region products when that response is generated against either trinitrobenzene sulfonate (TNBS)-modified cells or TNP-conjugated proteins. Human T cells can recognize TNP in association with determinants shared widely among other humans, polymorphic HLA-A and -B-locus-associated determinants distinct from HLA-A and -B. Studies of the cytotoxic responses of normal human lymphocytes to TNP-modified autologous cells have suggested that *Ir* genes control the response to TNP in association with human self-determinants. It is possible that TNP-modified tumor cells could be used to enhance immunity to unmodified tumor. (23 refs)

79-6083 The Role of Prothymocytes and the Thymic Microenvironment in the Pathogenesis of Thymic Lymphomas. (Eng) Waksal, S. D. (Tufts Cancer Res. Center, Tufts Univ. Sch. Medicine, Boston, MA); Robert, N.; Parkinson, D. R.; Morrissey, P. J.; Stout, R. D. *Proc Leukocyte Cult Conf* (12): 935-941; 1979.

Cell-to-cell interactions involved in prothymocyte/T-lymphocyte differentiation during the leukemogenic process were studied. After treatment with heterologous antiserum raised against mouse brain (anti-BAT serum) plus complement, the cytotoxic activity of untreated nu/nu spleen cells against RBL-5 lymphoma targets was dramatically reduced, whereas treatment with antiserum against

the alloantigen Thy 1.2 only partially reduced the cytotoxic activity. The expression of ecotropic virus in C57Bl/6 bone marrow after low level split dose irradiation was virtually abrogated after treatment with anti-BAT serum plus C'. The thymuses from young (6- to 8-wk-old) AKR mice expressed little gp70 on their surfaces, whereas thymocytes from 14- to 16-wk-old mice began showing increasing amounts, which finally resulted in expression on nearly all leukemic thymocytes. Similar expression was induced in C57Bl/6 thymocytes after a leukemogenic dose of radiation. AKR thymocytes cultured with thymus epithelium (TE) monolayers from young mice expressed high titers of ecotropic virus but no xenotropic virus. Cells cultured on TE monolayers derived from old AKR mice expressed not only high titers of ecotropic virus but also expressed xenotropic virus. This expression of xenotropic virus also appeared in vivo after 6 mo of age and was associated with events immediately preceding the appearance of thymomas. Thus, the appearance of xenotropic virus may be one of the co-factors required for leukemic transformation. The events associated with the differentiation of leukemic T-lymphocytes appear to involve a mosaic of interactions involving prothrombocytes, thymic epithelium, and endogenous C-type RNA viruses. (17 refs)

79-6084 HLA Alloantigens: Disease Association and Biologic Significance. (Eng) Mann, D. L. (Immunology Branch, NCI, NIH, Bethesda, MD 20205); Murray, C. *Semin Hematol* 16(4): 293-308; 1979.

Recent advances related to the association between human histocompatibility antigens (HLA) and disease are reviewed. The current concept of the fine structure of the human major histocompatibility complex (MHC) is discussed, as are investigations into some of the biochemical properties of MHC gene products. Data relating the recently described DRw antigens to specific disease states are also summarized, as are the results of some investigations into the functional properties of the MHC. Both the HLA and DRw antigens appear to play an important role in disease processes, and levels of two of the important complement components are coded for by genes of the MHC. Disease associations are high with the HLA-B locus antigens and even greater with the DRw antigens. Most diseases studied have a demonstrable component of autoimmunity, and complementation of action of a number of individual identical genes may give rise to the manifestation of the disease state. Different DRw antigens were shown to reflect clinical manifestation of two disease conditions: psoriasis and arthritis. However, these antigens have a common association and thus reflect or represent the common disease component in sicca syndrome. (98 refs)

79-6085 The Significance of Cancer After Renal Transplantation. (Eng) Montie, J. E. (Section Urology, Cleveland Clinic Foundation, Cleveland, OH 44106). *J Urol* 122(3): 298-299; 1979.

The significance of cancer development following renal transplantation is reviewed. This is a well documented occurrence and has immunologic implications. However, the incidence and severity of these malignancies are not of such a magnitude as to discourage the use of transplantation as a major treatment for chronic renal failure. Suppression of the immune surveillance system has been believed to be the cause of cancer after transplantation, but recent data suggest that this is not an adequate explanation. (9 refs)

- 79-6086 The Immune System of Animals and Its Role in Malignant Disease. (Ger) Pasternak, G. (No affiliation given). *Sitzungsber Akad Wiss DDR Math Naturwiss Tech* 6: 1-24; 1979.

Developments in the field of tumor immunology, particularly the search for a method of vaccination against cancer, are reviewed from 1953 to the present. The immunogenicity of chemically induced, transplantable tumors in an inbred mouse strain was shown in the early 1950's. Tumor-specific transplantation immunity induced in this animal model can be transferred to nonimmunized mice using lymphocytes from immunized mice. Tumors in different mice do not react with the same antigen even though the tumors were caused by the same carcinogen. Tumors induced by the same virus strain in different animals are antigenically cross-reactive, in contrast. Mechanisms of antigen recognition were studied extensively in the 1960's. The ability to produce antibodies appears to be genetically determined. Although immunization techniques developed in animals cannot ethically be directly applied to humans without further work, knowledge of immune systems has led to immunotherapy used with some success in human patients. Tumor antigens are currently used in diagnosis also. (33 refs)

- 79-6087 Molecular Approaches to Human Colon Cancer. (Eng) Kahan, B. D. (Dept. Surgery, Univ. Texas Medical Sch. at Texas, Houston, TX 77030); Rutzky, L. P.; Legrue, S. J.; Tom, B. H. In: *Oncodevelopmental Antigens*. Fishman, W. H., Busch, H., eds. (New York: Academic Press): Methods in Cancer Research Vol. 18, 409 pp.; 197-275; 1979.

Progress toward the elucidation of antigenic determinants that may provide a focus for measuring tumor-specific host immune performances and for designing and evaluating the results of immunotherapeutic maneuvers is reviewed. Despite chemotherapy, radiotherapy, and surgery, a large number of patients succumb to colon cancer. Immunotherapy offers the potential of harnessing the host immune response to control this neoplasm. In order to achieve a rational approach to specific immunotherapy, it is critical to define unique surface antigens distinctive for neoplastic cells. For this endeavor, the following are described: tissue-culture resources capable of cultivating a number of colonic cell lines and cloned subpopulations under a variety of conditions; chemical techniques to solubilize and purify membrane protein components; and immunologic tools to raise and characterize specific xenoantisera. Humoral factors controlling differentiation of colonic adenocarcinoma cells and of mediating intercellular adhesion are being investigated, utilizing hollow fiber tissue culture systems. Initial findings suggest the presence of unique tumor antigens that may represent suitable reagents for immunodiagnostic tools and for immunotherapeutic treatment modalities, in order to afford improved prospects for patient survival. (125 refs)

- 79-6088 Tumor Dormancy: A Review. (Eng) Alsabti, E. A. (Flat No. 5, Norfolk Terrace, Brighton BN1 3AD, England). *Tumor Res (Sapporo)* 13: 1-13; 1978.

The literature on tumor dormancy (TD), a state in which tumor cells persist in a clinically normal host for prolonged periods of time, is reviewed. Very few examples of TD have been demonstrated in animals, probably because of the short duration of most animal experiments. Maintenance of TD may involve the loss of exposed cell-surface targets for host effector mechanisms as

a result of antigenic modulation. During TD, oncogene expression may be suppressed by the action of host antitumor mechanisms acting at the cell surface, or alternatively, some surface receptors responsible for regulation of cell division that are usually concealed during tumor progression may become unmasked during antigenic modulation, leading to recovery of the control of cell division. Finally, TD could be established by the action of cytostatic rather than cytolytic host mechanisms. Tumor emergence (TE) may result from impairments in immune mechanisms due to senescence. The high incidence of TE during prolonged immunosuppression in humans is noteworthy. The low incidence of tumors in nude mice argues against this escape route, although B cells and macrophages in these mice may exert strong tumor-suppressive effects. Blockage of an effective host antitumor mechanism in vitro has also been proposed as a mechanism for TE in vivo. TE could also result from the absence of cell-surface tumor-associated antigens. In humans, the prolonged suppression of tumor metastasis and TD are probably mediated by a noncomitant immune response to tumor-associated antigens. TD can be diagnosed (1) prospectively by identifying tumor cells in tissue sections, isolating tumor cells from a host in clinical remission or identifying tumor markers such as carcinoembryonic antigen and (2) retrospectively by identifying emerging tumor cells as progeny of the original tumor cells. (66 refs)

- 79-6089 Teratocarcinoma and the Expression of Oncodevelopmental Genes. (Eng) Solter, D. (Wistar Inst. Anatomy and Biology, 36th and Spruce Sts., Philadelphia, PA 19104); Damjanov, I. In: *Oncodevelopmental Antigens*. Fishman, W. H., Busch, H., eds. (New York: Academic Press): Methods in Cancer Research Vol. 18, 409 pp.; 277-332; 1979.

Problems recently encountered in the study of teratocarcinoma are reviewed. Embryonal carcinoma cells are discussed with respect to their morphology, the origin of teratocarcinomas, teratocarcinoma-derived cell lines, and chromosomal studies of teratocarcinoma cells. The differentiation of embryonal carcinoma cells is also reviewed, with regard to somatic tissues, teratocarcinomas with a limited capacity for differentiation, yolk sac carcinomas, embryoid body formation, and the control of differentiation of embryonal carcinoma cells. Other topics include: the control of malignancy in embryo-derived teratocarcinomas; control of the expression of the malignant phenotype; and the products (surface, cytoplasmic and excreted, and nuclear proteins) of oncodevelopmental genes in embryonal carcinoma cells. (249 refs)

- 79-6090 Acute Myeloblastic Leukemia Considered as a Clonal Hemopathy. (Eng) McCulloch, E. A. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); Howatson, A. F.; Buick, R. N.; Minden, M. D.; Izaguirre, C. A. *Blood Cells* 5(2): 261-282; 1979.

Laboratory data on acute myeloblastic leukemia (AML) are reviewed from the point of view that AML is a clonal hemopathy. The hematologic findings in AML describe the cellular composition of one or, at most, very few abnormal clones. The marked patient-to-patient variation in marrow granulopoietic progenitor frequency might be a consequence of the stochastic nature of clonal expansion rather than the result of the transforming event. It is suggested that in AML, only leukemic clones or progressed subclones progress. The characteristics of colonies in mitogen-stimulated cultures of leukemic peripheral blood indicate that the cells of origin of such colonies are a subpopulation of leukemic

blasts. A model for the development of AML specifies that the emergence of a blast component in an abnormal clone marks the transition from preleukemia to leukemia. The blast cell populations appear to be maintained independently of the myelopoietic components of leukemic clones. This independence may be based on progenitor self-renewal. (50 refs)

- 79-6091 Contact Inhibition and Malignancy. (Eng) Abercrombie, M. (Strangeways Res. Lab., 'Worts' Causeway, Cambridge, England). *Nature* 281(5729): 259-262; 1979.

The role of contact inhibition in influencing the behavior of malignant cells is reviewed. Invasion in culture may be assessed by a method involving confronted cultures in which two foci of explants are placed about 1 mm apart. Normal mouse muscle fibroblasts confronted with chick heart fibroblasts show a very high degree of obstruction, the invasion zone having a width of 20 μ m. Confronting each of six tumors (mouse sarcomas 311, BAS56, S180, FS9, MCIM and a mouse melanoma) with the chick fibroblasts results in invasion zones 130-290 μ m wide. Studies using both static (overlap index) and dynamic (time-lapse filming) methods of assessing contact inhibition demonstrate that it is a general feature of normal fibroblast collision. A conspicuous feature of contact inhibition in fibroblasts is the contraction undergone by the cell's front end. In nonreciprocal contact inhibition, the cell that is not inhibited proceeds while the cell that is inhibited retracts. In a quantitative study of tumors using the overlap index, a broad range of indices was found (2%-91%), whereas the indices of nonmalignant cells were in the 3-19% range. Thus malignant cells are characterized by their broad variability compared to normal cells. It is not clear how a lowered homotypic contact inhibition of malignant cells contributes to their invasiveness. Both reciprocal and nonreciprocal invasion are exhibited by the various tumors studied. In addition to contact inhibition, variable adhesiveness might play a part in determining invasiveness; other factors may also play a minor role. (19 refs)

- 79-6092 DNA Repair Defects and Chromosome Instability Disorders. (Eng) Polani, P. E. (Prince Philip Res. Labs., Guy's Hosp. Medical Sch., London, England). *Ciba Found Symp* (66): 81-133; 1979.

The clinical, chromosomal, and general molecular aspects of four autosomal recessive disorders are reviewed: xeroderma pigmentosum (XP), Fanconi anemia (FA), ataxia telangiectasia (AT), and Bloom disease (BS). Between 80%-90% of XP patients have a defect, demonstrable at cellular level, of excision of DNA lesions induced by UV, while the remainder have a cellular error of postreplication repair. XP cells are also deficient in repairing DNA damage caused by some chemical mutagens. AT is heterogeneous clinically and genetically. It is characterized by γ -radiation sensitivity, which generally involves an inability to remove DNA lesions. In many cases, a chromosomally marked cellular clone is present. In BS there seems to be a defect consisting of slow DNA chain maturation during synthesis with the formation of an excessive number of sister chromatid exchanges. In FA, the cellular defect apparently consists of faulty removal or repair of cross-links in the DNA. All four disorders behave as rare autosomal recessives, and all are characterized by a tendency toward malignancy. Patients with XP develop skin cancers in early life and often malignant melanomas. In the other three disorders, leukemia and related proliferative disorders are a frequent cause of death. There is some evidence of an increased risk of malignancy in heterozygotes who carry the FA and AT genes. (12 refs)

- 79-6093 Multiple Endocrine Neoplasia. (Fre) Pradalier, A. (Service due Pr J. Dry, Hopital Rotschild, 43 bd de Picpus, 75012 Paris, France); Roger, M. *Med Int* 14(5): 329, 331-332, 334-338; 1979.

The literature on multiple endocrine neoplasia (MEN) is reviewed. Two types of MEN are distinguished. Wermer's syndrome accounts for approx 80% of all cases of MEN; it can involve the parathyroid gland, pancreas, and less often, the pituitary gland, and is often associated with carcinoid tumor, mainly in the lungs. Sipple's syndrome involves medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid tumor. The hypothesis attributing MEN to the hyperfunction of the parathyroid gland, islands of Langerhans, and pituitary gland has not been confirmed. According to one plausible hypothesis, MEN is genetically determined by a pleiotropic gene with autosomal dominant heredity and variable degrees of expression. According to another hypothesis, MEN is considered a dysplasia of the neuroectodermal tissue. (33 refs)

- 79-6094 Pathology of Gastric Carcinoma. (Fle) Geboes, K. (Laboratorium voor Histochemie en Cytochemie, A.Z. St. Rafael, Louvain, Belgium); Desmet, V. *Tijdschr Gastroenterol* 21(5): 367-378; 1979.

The pathology and classification of gastric carcinoma are reviewed. The presence of precancerous lesions implies an increased risk of malignant transformation. These lesions include gastric polyps, mucosal alterations in pernicious anemia, and intestinal metaplasia. The risk of gastric cancer is also increased after partial gastrectomy. Carcinoma in situ consists of malignant cells without signs of invasion. The differential histological diagnosis of carcinoma in situ, epithelial atypia, and adenoma may be difficult. (21 refs)

- 79-6095 A Rationale for the Loss of Growth Control During Experimental Bladder Carcinogenesis. (Eng) Reese, D. H. (Dept. Urology (D-1), Univ. Miami Sch. Medicine, P.O. Box 016217, Flagler Station, Miami, FL 33101); Politano, V. A. *Med Hypotheses* 5(9): 1007-1015; 1979.

The loss of growth control associated with the early phase of experimentally induced bladder cancer is reviewed, and an explanation for this phenomenon is offered. It is proposed that the focal loss of alkaline phosphatase activity and increased cell proliferation occurring in urothelium following exposure to carcinogens are manifestations of a defective interaction between glucocorticoid hormone and urothelium, and that this defect is an underlying cause for the loss of growth control occurring during bladder carcinogenesis. In this manner, the urothelium loses, at least temporarily, the ability to respond to glucocorticoid hormone; this phenomenon may involve a defect in the receptor mechanism. The underlying cause of other benign proliferative lesions of the urothelium could also be the defective interaction between glucocorticoid and urothelium. The defect in these cases would be reversible. The appearance of a defect in the interaction between glucocorticoid and urothelium could, therefore, be a common response to injurious agents and may be part of a mechanism that facilitates regenerative hyperplasia following urothelial injury. (54 refs)

- 79-6096 Neuroendocrinological Aspects of Ovarian Tumors as Dissipative Structures. (Pol) Klimek, R. (Klinika En-

dokrynologii, Instytut Ginekologii i Poloznictwa AM, ul. Koper-nika 23, 31-501 Krakow, Poland). *Patol Pol* 30(2): 187-193; 1979.

The thermodynamic model of neoplastic processes is discussed with special reference to ovarian tumors. In contrast to other diseases, the formation of biologically dissipative structures in the course of carcinogenesis is the essence of the neoplastic process. The development of these structures is linked to the dissipation of energy and matter from other parts of the body, which markedly enhances entropy and thus leads to early death and to the depletion of the body's source of energy and matter. (7 refs)

- 79-6097 Occupational Health and Coal Conversion. (Eng) Young, R. J. (Natl. Inst. Occupational Safety and Health, Cincinnati, OH); Evans, J. M. *Occup Health Saf* 48(6): 22-26; 1979.

Epidemiologic evidence indicates that workers routinely exposed to products of combustion or distillation of bituminous coal are at increased risk of developing cancers of the skin, lungs, urinary tract, larynx, nasal sinuses, stomach, intestine, pancreas, and hematopoietic organs. The National Institute for Occupational Safety and Health has made a first attempt to develop occupational health and safety for the US Synthetic Fuels Program. The use of pilot and demonstration plants in such an undertaking are discussed. Occupational health and safety must be given adequate consideration in the developmental stages of coal conversion. (33 refs)

- 79-6098 The Role of Fusarium Mycotoxins in the Aetiology of Tumours of the Digestive Tract and of Certain Other Organs in Man and Animals. (Eng) Schoental, R. (Dept. Pathology, Royal Veterinary Coll., Univ. London, London, England). *Front Gastrointest Res* 4: 17-24; 1979.

The possible role of Fusarium mycotoxins in the etiology of human and animal tumors is reviewed. Some diseases and tumors of the digestive tract in man and lower animals may be caused by trichothecenes (eg, T-2 toxin), the irritant secondary metabolites of Fusaria and other species of field fungi which contaminate cereals and other foodstuffs. The estrogenic metabolites of Fusaria, including zearalenone, may be involved in abnormalities and neoplasias of the gonads and related organs. The reported unpredictable variations in the incidence of tumors in laboratory rats, mastomys, and mice might be explained by occasional heavy contamination of the diet with mycotoxins. T-2 toxin may also be involved in the etiology of diseases and tumors considered as spontaneous in various species, including man. T-2 toxin could be effective per se or, acting in conjunction with other factors, could contribute to the multifactorial origin of cancer. (32 refs)

- 79-6099 Epidemiological Features of Gastrointestinal Cancer. (Eng) Burkitt, D. P. (Unit Geographical Pathology, St. Thomas's Hosp., London SE1 7EH, England). *Front Gastrointest Res* 4: 86-95; 1979.

The epidemiological features of various gastrointestinal cancers are reviewed. Tumors in different parts of the alimentary tract have characteristic different geographical, ethnic, sexual, and socioeconomic distributions. Among the oral cancers, epithelioma of the cheek is closely associated with the chewing of pan leaf in

which substances such as lime, tobacco, and betel-nut are folded. Esophageal cancer, which shows variations in incidence associated with geography, ethnic background, and sex, may be caused by different factors in different geographical regions. The etiology of gastric cancer, which also varies with geography, ethnic background, and sex, is also as yet undetermined. Primary liver cancer exhibits a high prevalence over much wider geographical regions than do esophageal or gastric cancer. Current evidence suggests that both aflatoxin and hepatitis B infection may be involved in its etiology. The incidence of colorectal cancer varies according to the extent of economic development and the influence of modern western culture. Both excessive consumption of fat and insufficient fiber may play a role in the pathogenesis of this cancer. (52 refs)

- 79-6100 Gastrointestinal Cancer. Genetics and Genetic Markers. (Eng) McConnell, R. B. (Broadgreen Hosp., Thomas Drive, Liverpool, L14 3LB, England). *Front Gastrointest Res* 4: 134-141; 1979.

The influence of heredity on the etiology of gastrointestinal (GI) cancer is reviewed. This influence can be considered under four headings. Dominant inheritance with high cancer risk is seen in individuals with tylosis, polyposis coli, discrete colonic polyps, and 'cancer family' syndrome. The GI cancers in such individuals develop due to the effects of a single gene in a Mendelian dominant manner. The following five conditions are also inherited in a dominant manner and are associated with a less marked but nevertheless significantly increased cancer risk: hereditary pancreatitis, Peutz-Jeghers syndrome, hemochromatosis, Wilson's disease, and multiple endocrine adenomatosis. In the following conditions, inheritance is probably multifactorial due to the effect of several genes plus a considerable environmental influence: pernicious anemia, celiac disease, Crohn's disease, ulcerative colitis, chronic calcifying pancreatitis, and cirrhosis of the liver. In addition, the relatives of persons with stomach cancer are at increased risk for this disease, as are persons of blood Group A. A four-fold increase in the risk of colon cancer was found among relatives of persons with colon cancer and among relatives of persons with ulcerative colitis or Crohn's disease. (23 refs)

- 79-6101 Carcinogenesis of Gastrointestinal Cancer. (Eng) Hill, M. J. (Central Public Health Lab., Colindale Ave., London NW9, England). *Front Gastrointest Res* 4: 1-16; 1979.

Epidemiological studies of gastric and colorectal cancer, the concepts of carcinogenesis evolving from these studies, and data for and against the hypotheses are reviewed. A correlation between nitrate intake and gastric cancer incidence has been demonstrated in Colombia and suggested in Japan. A model has been proposed for gastric carcinogenesis which involves a series of mutations and cell transformations leading to gastric metaplasia and then to carcinoma and mediated by nitrosamines or N-nitroso compounds formed endogenously. Studies of colorectal cancer tend to support a correlation with fat or meat intake, but the results are not conclusive. Three diseases predispose to colorectal cancer: adenomatosis coli, ulcerative colitis, and single or multiple adenomas. Other cancers, eg, cancer of the breast, endometrium, ovary, and prostate, which have been postulated to have a steroid hormonal etiology, are associated with colorectal cancer; thus the latter may also have a steroidal etiology. Evidence for a causal role for bile acids in colorectal cancer has been obtained from studies of several populations, but the nature of the bacterial metabolite

involved is not clear. Most, if not all, colorectal carcinomas arise in preformed adenomas; the risk of carcinoma development depends therefore on the risk of developing adenoma and on the risk of that adenoma progressing to malignancy. In both gastric and colorectal cancer, multi-step etiologies have been proposed that are suitable to experimental verification. (73 refs)

- 79-6102 Current Trends in Toxicological Research. (Eng) Allison, A. C. (Cell Pathology Div., Clinical Res. Centre, Harrow, Middlesex, England). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 387-401; 1978.

Current trends in toxicological research are reviewed. Topics include interactions of toxins with membranes, carcinogens and the lung, effects of inhaled polyvinyl chloride particles, analytical electron microscopy of toxic dusts, the toxic effects of asbestos, the effects of silica and asbestos on macrophages, tests with cell cultures as predictors of toxicity, granulomatous reactions, trends in academic toxicology research, and the applications of toxicology research. Carcinogen metabolism in vivo and enzymatic repair of carcinogen-induced damage are discussed. (31 refs)

- 79-6103 A New Theory of Carcinogenesis. (Eng) Holliday, R. (Natl. Inst. Medical Res., The Ridgeway, Mill Hill, London NW7 1AA, England). *Br J Cancer* 40(4): 513-522; 1979.

A new theory of carcinogenesis is proposed. Although many carcinogens are mutagens, there is no direct evidence that the cancer-cell phenotype is the result of gene mutation and malignant cells can arise or revert to the normal phenotype in the absence of mutation. It is suggested that damage to DNA followed by repair triggers the epigenetic changes in gene expression responsible for malignancy. It was previously suggested that methylation of specific DNA sequences adjacent to structural genes determines whether or not transcription will occur and that specific methylases provide a basis for the control of gene expression in differentiated cells. It is now known that damage to DNA followed by repair, just before or just after DNA replication, can lead to the loss of methyl groups. This can induce a switch in gene activity that is heritable but potentially reversible. This theory accounts for the known large difference in the probability of malignant transformation in cells of rodents and large mammals. There is evidence that excision repair is more efficient in cultured fibroblasts from large long-lived animals than from small short-lived ones. (58 refs)

- 79-6104 Impact on Drugs, Food, and Environment. (Eng) Worden, A. N. (Huntingdon Res. Center, Huntingdon, Cambridgeshire, England). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 415-434; 1978.

Modifications based on toxicological research could help to diminish hazards such as those associated with smoking, including carcinogenicity. Cancer associated with inhalation of combustion

products containing known carcinogens has decreased in the United Kingdom since 1955, and the hazards of exposure to mesothelioma-inducing asbestos particles could be reduced by reducing cigarette smoking. The predictive use of animal experimentation must be linked with postmarketing or postexposure monitoring and surveillance. Among the human environmental carcinogens that have been "predicted" from animal experimentation are mustard gas, vinyl chloride, stilbestrol, and aflatoxin. Foods constitute the most complex group of substances from the standpoint of predictive toxicology. It is suggested that although toxicity testing might delay and add to the expense of the clearance of new medicines, it does not ultimately deprive mankind of valuable therapeutic agents. (85 refs)

- 79-6105 Toxicological Aspects of the Air We Breathe. (Eng) Lawther, P. J. (M.R.C. Toxicology Unit, Clinical Section, St. Bartholomew's Hosp., London, England). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 15-34; 1978.

Toxicological evaluations of air pollutants, especially in the United Kingdom, are reviewed. Since passage of the Clean Air Act (1966), a series of studies suggests that the concentration of benzo(a)pyrene (BP) in the air is 1/10 of what it was 25 yr ago. There are also signs that the urban excess of lung cancer is declining. An association has been found between occupation in or residence near asbestos works and pleural mesothelioma. There is evidence that exposure need be only minute and that the resulting tumors may not be clinically manifest for up to 40 yr. Urban air contains many metals in trace amounts, some of which have been associated with cancer among occupational groups, eg, nickel, chromium, and beryllium. Concern about pollution of the communal air by industrial carcinogens has also been stimulated by the induction of angiosarcoma in workers using vinyl chloride monomer. Carbon monoxide exerts deleterious effects on the CNS and cardiovascular system. The effects of high doses of lead in adults and children are well-known, but there is conflicting evidence about the subclinical effects of body burdens formerly thought to be insignificant. (49 refs)

- 79-6106 Some Remarks on General Principles for Prevention of Toxic Hazards. (Eng) Truhaut, R. (Centre de Recherches Toxicologiques de la Faculte des Sciences Pharmaceutiques et Biologiques, Universite Rene Descartes, Paris, France). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 369-380; 1978.

The role of toxicology as a preventive science is emphasized. Toxicological evaluation is achieved in three steps: (1) collection and (2) interpretation of facts, and (3) decision-making. The first stage should involve collaboration between experimental toxicologists and clinicians and/or epidemiologists. While the ideal rule for prevention would be to exclude hazardous chemicals from the environment, such measures are not always possible; but the amount of pollutants to which people are exposed should be reduced as much as possible. In the case of industrial chemicals of high toxicity, efforts should be directed at replacing them with functionally equivalent chemicals which are nontoxic or at least much less toxic. Very often, the toxicity of a substance may be due to the im-

purities it contains; thus rigorous purity standards should be enforced. The determination of thresholds and permissible limits is important for occupational chemicals, atmospheric pollution, and food additives. The promotion of suitable health education for exposed individuals and particularly for those in the chemical industry is stressed. (13 refs)

- 79-6107 Toxicology in a Cold Climate. (Eng) Somers, E. (Environmental Health Directorate, Health Protection Branch, Dept. Natl. Health and Welfare, Ottawa, Canada). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 75-86; 1978.

The role of toxicology in evaluating environmental hazards and setting standards in Canada is discussed. Evaluation of human health hazards is based on the following: (1) concentration of the substance to which man is exposed; (2) toxic properties of the substance; (3) stability of the substance in the environment and in tissues; (4) accumulation in tissues; and (5) interactions with other substances. There are two options for achieving control over a potentially hazardous environmental agent: (1) restriction of the release of the agent, eg, setting emission standards for air or water; and (2) control of the agent itself. Risk-cost-benefit considerations, in spite of their limitation, have a useful place in decisions relating to the choice of regulatory strategies. Risk-benefits assessments made in Canada in recent years are illustrated by the establishment of a guideline for the mercury content in fish and by the conclusion that present levels of use of nitrilotriacetic acid in detergents do not pose an unacceptable health hazard to the public. (10 refs)

- 79-6108 General Principles of Preventive Toxicology. (Eng) Izmerov, N. F. (Inst. Industrial Hygiene and Occupational Diseases, Moscow, USSR); Sanotski, I. V. In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 359-368; 1978.

General principles of preventive toxicology are reviewed. A variety of theoretical investigations, principles, and methods for the evaluation of toxicity have been developed, including the principle of synchronization of toxicological investigations with the stages of technological development and production of new compounds. The stage investigation principle allows evaluation of chemical substances and technological processes before their use in production and distribution in the environment. The principle of threshold for all forms of chemical events (such as mutagenesis and carcinogenesis) and the principle of unity of molecular, structural, and functional changes as the basis for differentiation between effect and harmful effect are discussed. (9 refs)

- 79-6109 Toxicological Aspects of the Water We Drink. (Eng) Benes, V. (Inst. Hygiene and Epidemiology, Prague, Czechoslovakia). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 35-45; 1978.

Current approaches to the assessment of toxic risk posed by trace chemical substances in drinking water are reviewed. Acceptable daily intake (ADI) values may be useful in considering possible risk from pesticide residues in drinking water. However, ADI values have not been established for a number of substances. In these cases, a preliminary risk assessment is made by comparing actual intake with available toxicological data. Exposure to polychlorinated biphenyls via drinking water (2 nanograms/liter) can be considered relatively slight provided further contamination does not occur. For carcinogenic polycyclic aromatic hydrocarbons (PAH) the limit of 0.2 µg/liter has been derived from the background levels in ground water. PAH are present in the soil and vegetables as well as in water. For the cumulative metals (lead, mercury, and cadmium) only provisional tolerable weekly intakes for humans have been estimated: for lead, 50 µg/kg; for mercury, 5 µg/kg; and for cadmium, 6.7-8.3 µg/kg. Zinc, selenium, and cobalt appear to exert a protective effect against the toxicity of cadmium and mercury. This interaction makes it important to consider simultaneous exposure to these elements for accurate assessment of risk. A serious problem is associated with the presence of nitrates in drinking water since this contamination may lead to the formation of N-nitroso compounds. Trace amounts of N-nitroso pesticide derivatives have been found in the drinking water of one US city. Assessment of possible human carcinogenic risk from chlorinated hydrocarbons in drinking water is difficult due to limited data from experimental studies and lack of appropriate epidemiological studies. (60 refs)

- 79-6110 Toxicological Aspects of the Food We Eat. (Eng) Poulsen, E. (Inst. Toxicology, Natl. Food Inst., Copenhagen, Denmark). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 47-59; 1978.

Methods used in evaluating food toxicity are reviewed; and natural food components, food additives, and food contaminants are considered in relation to toxicology. Toxicological studies required to evaluate food safety and to estimate an acceptable daily intake (ADI) for humans include acute toxicity tests, short- and long-term studies in animals, and observations in humans wherever possible. The evaluation of nitrates and nitrites as food additives illustrates the way toxicology has tried to fulfill its role as a predictive science. Nitrite can convert certain nitrogen-containing compounds to N-nitroso compounds, many of which are carcinogenic in low doses in a variety of animal species. It must be assumed that these compounds are generally carcinogenic in man. Studies have recently indicated that nitrate levels in certain vegetables (spinach, lettuce, celery) and drinking water may also present a potentially serious problem. The level of nitrite in the saliva is significantly higher and the blood content of nitrosamines is increased following ingestion of these high-nitrate foods. Butylated hydroxytoluene (BHT), a widely used food antioxidant, increased the incidence of lung tumors induced by diethylnitrosamine and by urethane in mice. The effect of BHT in animal experiments is influenced by the amount and relative concentrations of normal dietary components, eg, protein and fat. (33 refs)

- 79-6111 Environment and Cancer. (Spa) Francia Vina, J. M. (Centro Demostracion Sanitaria, Talavera de la Reina, Toledo, Spain); de la Pena de Torres, E. *Rev Sanid Hig Publica (Madr)* 52(11/12): 1435-1454; 1978.

This review of studies concerning environmental carcinogens includes investigations of geographic variations in cancer incidence, immigrant studies, and laboratory data on environmental carcinogens. The major environmental carcinogens are the aflatoxins, polycyclic aromatic hydrocarbons, nitrosamines, UV rays, and ionizing radiation. In humans, the effective and ineffective doses of chemical carcinogens have not yet been established. It is difficult to assess the significance of additional exposure to ubiquitous environmental carcinogens, such as polycyclic aromatic hydrocarbons, nitrosamines, and mycotoxins. In 1976, the cancer mortality in Oviedo Province amounted to 1,862 cases (1,060 men and 802 women). Stomach cancer accounted for 16.5%, lung cancer for 16.1%, small intestinal cancer for 3.8%, colorectal cancer for 5.8%, liver and gallbladder cancer for 8.7%, pancreatic cancer for 2.8%, cancer of other gastrointestinal organs for 2.3%, laryngeal cancer for 3.1%, urinary bladder cancer for 1.6%, renal cancer for 2.2%, prostate cancer for 5.9%, breast cancer for 6.3%, uterine cancer for 2.4%, ovarian cancer for 1.9%, brain tumors for 2.3%, bone tumors for 0.85%, malignant hematological diseases for 8.5%, buccal and pharyngeal tumors for 2.4%, esophageal tumors for 2.3%, and other tumors for 5.6%. (no refs)

- 79-6112 World PCBs MAP: Storage and Effects in Man and His Biologic Environment in the 1970s. (Eng) Wassermann, M. (Dept. Occupational Health, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Wassermann, D.; Cucos, S.; Miller, H. J. *Ann NY Acad Sci* 320: 69-124; 1979.

The epidemiologic features of the polychlorinated biphenyls (PCBs) stored in human tissues and in the biologic environment are reviewed, as are some of the effects of PCBs. Information concerning PCB residues in marine organisms, fresh water and marine fish, birds, avian eggs, terrestrial animals, the adipose tissue of the general human population, and human plasma and milk is presented. The effects of PCBs on reproduction in aquatic organisms, birds, and terrestrial mammals are discussed, as are the effects of these compounds on development and growth, liver morphology, enzyme activity, drug and lipid metabolism, liver porphyrins, hormones, the immunologic defense system, and the nervous system. Also discussed are the dermatologic and tumorigenic effects of PCBs. Hepatocellular adenomas, carcinomas, and adenofibrosis have been induced by commercial mixtures of PCBs and pure biphenyl compounds in mice; these neoplasms have also been induced in rats by technical mixtures of PCBs. Tumor incidence increases with dosage. PCBs may act as promoters of experimental liver carcinogenesis in some cases and may inhibit carcinogenesis associated with some promoters (eg, diethylnitrosamine). These compounds have caused hyperplasia of hair follicle epithelium and severe hypertrophic and hyperplastic gastritis in adult monkeys. Malignant melanomas have been found in 2/31 persons in one group and 1/41 persons in another group of individuals exposed occupationally to PCBs. However, these workers were also exposed concomitantly to other carcinogens, particularly epoxides. (340 refs)

- 79-6113 Environmental Cancer: Interplay Between Laboratory and Field Studies. (Eng) Nelson, N. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY). In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March-2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 327-337; 1978.

The respective roles of epidemiologic and laboratory studies in identifying specific factors leading to a particular cancer are reviewed. The alkaline chromates have been identified as the agents of probable greatest importance in cancer induction by chromium. Extensive epidemiologic studies on the consequences of childhood scalp irradiation for control of ringworm were augmented by laboratory studies that identified the dose to various biological targets from the procedure. These studies led to the identification of eight thyroid adenomas in 1,500 children exposed at the very low dose of 6 rads to the thyroid. Cigarette smoking has been linked to lung cancer in many studies, but the specific carcinogenic factors have not yet been identified precisely. Cigarette smoke contains promoting and cocarcinogenic agents that substantially enhance the activity of the carcinogenic polynuclear hydrocarbons, and the combination of all these factors may produce the carcinogenic effects of cigarette smoke. Vinyl chloride and bis(chloromethyl)ether were identified as carcinogens in the laboratory in the absence of epidemiologic evidence. Subsequently, definitive epidemiologic studies confirmed that occupational cancers had resulted from exposure to these chemicals. A clear association was established between lung cancer and occupational exposure to the chloroethers. Dimethyl carbamoyl chloride has also been identified as carcinogenic in related studies. (22 refs)

- 79-6114 Need to Pursue New Leads in the Epidemiology of Colorectal Cancer. (Eng) Graham, S. (Dept. Sociology, State Univ. New York at Buffalo, Buffalo, NY 14261); Haenszel, W.; Bock, F. G.; Lyon, J. L. *J Natl Cancer Inst* 63(4): 879-881; 1979.

The literature concerning the epidemiology of colorectal cancer (CRC), particularly that concerning the relationship between diet and cancer, is reviewed, and the need for further research is stressed. A clear case has not been established for the theories that the risk of CRC is related to decreased fiber and increased fat consumption. There have been few epidemiologic studies, and most that have been done have involved small numbers of subjects. An investigational model involving a prospective study of normal persons is needed. Since such a model would involve questioning subjects regarding dietary habits, further research on the validity of interviewing in regard to diet is required. Specific animal studies of CRC and epidemiologic interview and questionnaire studies cannot establish a protective effect for cruciferous vegetables. Epidemiologists should examine the possible factors that could inhibit CRC development and should use the more traditional approach of seeking factors that might predispose to its development. (40 refs)

- 79-6115 Occupational Lung Disease: How Significant a Problem? (Eng) Strasser, A. L. (Dept. Community Health and Occupational Medicine, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY). *Occup Health Saf* 48(6): 16-19; 1979.

The significance of occupational lung disease is reviewed, with emphasis on the occurrence of black lung, asthma, and lung cancer among those employed in particular occupations. Lung cancer causes more deaths in men than any other malignancy, and its incidence is increased among workers exposed to asbestos, arsenic, or chromates. The incidence of occupational lung cancer can be reduced by good pre-placement examinations and standards, good industrial hygiene and proper ventilation, and elimination of smokers from occupations involving exposure to certain chemicals. (no refs)

- 79-6116 Case-Control Studies on the Effect of Sex Steroids on Women and Their Offspring. (Eng) Janerich, D. T. (Cancer Control Bureau, New York State Dept. Health, Albany, NY 12237); Glebatis, D.; Flink, E.; Hoff, M. B. *J Chronic Dis* 32(1/2): 83-88; 1979.

The use of the case-control method for studies of birth defects and breast tumors in relation to exposure to female sex hormones is discussed. Case-control studies are the strongest analytic epidemiological tools for the study of causal mechanisms of diseases that are rare or that have long latency periods, but they have two major handicaps: (1) relative risk is expressed in terms of exposure among the diseased; and (2) exposure is ascertained after the disease has occurred. Both of these handicaps can be overcome by careful study design. In an ongoing case-control study of breast disease and oral contraceptive use, two characteristics were considered potential confounding factors: (1) the dramatic increase in oral contraceptive use in the mid-1960's; and (2) the protective effect of early first pregnancy against breast cancer. A preliminary case-control study confirmed the importance of considering age at first pregnancy as a risk factor in young women and indicated that male first offspring had a greater effect on the risk associated with age at first pregnancy than female first offspring. Based on this information, the study of the role of oral contraceptives in breast cancer was designed so that the controls were matched by present age and age at first birth. The potential confounding effects of benign breast disease and sex of the offspring will be dealt with in the analysis of the data. (15 refs)

- 79-6117 A Review of the Epidemiology of Human Breast Cancer. (Eng) Kelsey, J. L. (Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 60 College St., New Haven, CT 06510). *Epidemiol Rev* 1: 74-109; 1979.

Major aspects of the epidemiology of breast cancer are reviewed. The annual age-adjusted incidence and mortality rates for breast cancer among women in the US for 1973 through 1976 were 84.9 and 27.7 per 100,000 women, respectively. Both incidence and mortality rates vary greatly throughout the world, and within the US, rates are higher in urban than in rural areas and in the North as compared to the South. Tumors occur more frequently in the left breast than in the right. Large relative risks of breast cancer are associated with increasing age, a history of bilateral premenopausal breast cancer in a first degree relative, a history of breast cancer in the contralateral breast, and residence from an early age in North America compared with residence in Asia. Moderate relative risks are associated with previous oophorectomy, increasing age at first birth, a history of fibrocystic breast disease, previous exposure of the chest to high levels of radiation, a history of breast cancer in any first degree relative, obesity, and previous cancer in the ovary or endometrium. Age at menarche, age at menopause, marital status, place of residence, and race are associated with small but real differences in risk. The relative rarity of breast cancer in men makes it difficult to identify any but the strongest risk factors in this group. (358 refs)

- 79-6118 Cervical Carcinoma Today: New Aspects of Diagnosis and Treatment. (Ger) Pfleiderer, A. (Universitäts-Frauenklinik, Hugstetter Strasse 55, D-7800 Freiburg i. Br., W. Germany). *Ther Umsch* 36(6): 484-490; 1979.

Contemporary diagnostic and therapeutic aspects of carcinoma of the uterine cervix are discussed. Cervical carcinoma is the second most frequent carcinoma in women, and it is the most frequent

carcinoma in women aged <40 yr. In 1976, the incidence of cervical carcinoma (including carcinoma in situ) was 45/100,000 in South Wurttemberg-Hohenzollern, and 66/100,000 in the age bracket 30-35 yr. In 1976, 2,241 cases of malignant tumors of the uterine cervix were diagnosed in Baden-Wurttemberg; 1,034 of them were in situ carcinomas. The incidence of cervical dysplasia is highest in the age bracket 25-30 yr; that of carcinoma in situ, in the age bracket 35-40 yr; that of microcarcinoma, in the age bracket 40-45 yr; and that of invasive carcinoma, in the age bracket 56-67 yr. Cervical carcinoma can develop at the boundary between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervix. Smegma (probably due to the presence of certain proteins or viruses, eg, herpesvirus) or sperm can lead to a malignant transformation of the reserve cells especially in very young women (under the age of 17 yr). The retracting epithelium is replaced by metaplastic squamous epithelium in which the malignant transformation takes place (atypical metaplasia). Dysplasia can develop after a few years. In many cases, the dysplastic epithelium can degenerate and be rejected and replaced by normal epithelium. (no refs)

- 79-6119 Ovarian Carcinoma. (Ger) Spechter, H. J. (Abteilung Geburtshilfe, Städtisches Krankenhaus, Robert-Koch-Strasse 1, D-8003 Landshut, W. Germany). *Ther Umsch* 36(6): 518-523; 1979.

The incidence, etiology, pathology, and attempts at early diagnosis of ovarian carcinoma are reviewed. Mortality from ovarian carcinoma varies with location (deaths/100,000 women, 1.7 in Japan vs 11 in Denmark), but the causative factors have not been clarified. Ovarian tumors can be divided into epithelial and special types (eg, germ-cell, connective tissue, adrenal-rest cell tumors); each type includes many subtypes. The serosal tumors grow and metastasize much faster than the mucinous and endometrial carcinomas. Thus the prognosis varies with the tumor type. Only the hormonally active tumors that lead to irregular or postmenopausal bleeding are often diagnosed at early stages. Most patients have no characteristic symptoms until their ovarian malignancy is advanced. No screening test (cytological smear, blood antigen) has yet proven reliable for early diagnosis. (29 refs)

- 79-6120 Ovarian Tumors after Hysterectomy. (Ger) Roemer, V. M. (Universitäts-Frauenklinik, Tübingen, W. Germany); Neeser, E.; Peters, F. D.; Wehle, H. E. *Gynaekol Rundsch* 19(Suppl. 1): 107-123; 1979.

The incidence of ovarian tumors in hysterectomized women is reviewed. The advisability of prophylactic ovariectomy during hysterectomy is discussed. Calculations indicate that if bilateral ovariectomies (BLO) were routinely performed on women over 40 yr of age who were undergoing hysterectomy for benign disease, the incidence of ovarian carcinoma could be reduced approx 20%. These calculations also indicate that at least 700 BLO would be required to prevent 1 ovarian carcinoma. The psychological and physiological consequences of prophylactic ovariectomy must be considered before such a procedure is recommended. The incidence of ovarian tumors (benign or malignant) is apparently not greater in women who have undergone simple hysterectomy than in the general population. The calculated effect of prophylactic BLO depends on many variables, including age at which hysterectomy is done, frequency of hysterectomy in the population, and incidence of ovarian carcinoma. This incidence (per 100,000 population) varies from 2.8 in Japan to 15 in Scandinavia and increases

markedly with age at least to 80 yr. The av age at diagnosis is approx 60 yr. As a result of these considerations, routine ovariectomy (adnexectomy) is recommended for women undergoing hysterectomy after 50 yr of age and may be advisable for younger women who are considered to have an increased risk of ovarian carcinoma. Estrogen substitution therapy is recommended if premenopausal hysterectomy is done. Although the risk of breast cancer may be slightly increased in women on this therapy, at least one study shows their life expectancy to be greater than that of women with intact genitals and no hormone therapy. (76 refs)

79-6121 Ovarian Tumors with Special Reference to Dogs. (Pol) Zembrzycka, H. (Instytut Chorob Niezakażonych, Wydział Weterynaryjny SGGW-AR, ul. Grochowska 272, 03-849 Warsaw, Poland). *Patol Pol* 30(2): 245-251; 1979.

Ten ovarian tumors observed in dogs at a Veterinary Institute during a 10-yr period are described. Cystadenoma was diagnosed in 6 dogs aged 3-12 yr, cystadenocarcinoma in 2 dogs aged 8 and 12 yr, respectively, theca-cell tumor in a 6-yr-old dog, and cystadenoma in another 6-yr-old dog. A review of the literature shows that ovarian tumors account for about 1.4% of all tumors in dogs, compared with 1.8% in horses, and <0.7% in pigs, and 4% in ruminants in general. There is a species-specific predisposition to certain types of ovarian tumors in animals; the most frequent ovarian tumors are granulosa-cell tumors in cattle, granulosa-cell tumors and cystadenoma in dogs, and teratoma in horses. Although ovarian tumors occur in animals at all ages, the risk increases with age. (9 refs)

79-6122 The Drama of Ovarian Carcinoma. (Ger) Hauser, G. A. (Frauenklinik des Kantonsspitals, CH-6004 Lucerne, Switzerland). *Ther Umsch* 36(6): 532-537; 1979.

The general epidemiologic and diagnostic problems encountered with ovarian carcinoma are reviewed. Ovarian carcinoma accounts for about 20% of all carcinoma of the genitals, but it has the most unfavorable prognosis of all these tumors; the cure rate is only 24%. Menopausal bleeding, postmenopausal ovary syndrome, and a small number of childbirths imply increased risk of ovarian carcinoma. (11 refs)

79-6123 Epidemiology and Pathology of Ovarian Carcinoma. (Ger) Torhorst, J. (Institut für Pathologie der Universität Basel, Schönbeinstrasse 40, CH-4056 Basel, Switzerland); Almendral, A. C. *Ther Umsch* 36(6): 524-531; 1979.

The epidemiology and pathology of ovarian carcinoma are reviewed. Ovarian carcinoma accounts for approx 80% of all malignant ovarian tumors. The incidence (per 100,000 women) shows great geographic differences, ranging from 2.8 in Japan to 15.1 in Sweden, and it is substantially higher in Europe and North America than in Asia, Africa, and South America; thus the involvement of environmental factors is indicated. The incidence increases in Japanese women immigrating to the US. The frequent involvement of both ovaries, especially around menopause, suggests the role of an endocrine factor. Recent epidemiological studies have failed to demonstrate any relationship between ovarian carcinoma and either parity, abortion, or breast-feeding habits. No relationship has been found between ovarian carcinoma and exogenous hormone supply. The incidence is higher among single women and among members of the higher socioeconomic

strata, as well as among women with blood type A. The hazard of tumor induction by ionizing radiation appears to be negligible. Occupational exposure to asbestos and talc can be considered possible causes of ovarian carcinoma. The high frequency noted for the development of ovarian carcinoma subsequent to the onset of breast carcinoma suggests common or similar etiological factors. The mortality ranges from 1.7/100,000/yr in Japan to 11.1/100,000/yr in Denmark. (12 refs)

79-6124 Clinical Aspects of Endometrial Carcinoma. (Ger) Haldemann, R. (Universitäts-Frauenklinik, Schanze-neckstrasse 1, CH-3012 Bern, Switzerland). *Ther Umsch* 36(6): 506-510; 1979.

The incidence, epidemiology, and diagnosis of endometrial carcinoma (ENC) are reviewed. Conditions associated with increased risk of ENC include hypertension, diabetes mellitus, obesity, late menopause, menstrual disorders, and sterility. A disturbance of estrogen metabolism appears to underlie several of these risk factors. About 85% of ENC cases are found in postmenopausal women. An av age at diagnosis of 62 yr has been reported. Moderate obesity results in a risk factor (RKF) of 3, and RKF's as high as 9 have been found for extreme obesity. Histories of menstrual disturbances associated with overproduction of estrogen are reported by most patients, and a retrospective study indicated that about 80% have a glandular-cystic or adenomatous hyperplasia that can be considered a forerunner of ENC. Increased incidence of ENC is associated with increased socioeconomic status. The main symptoms of ENC are menstrual disturbance in premenopausal women and uterine bleeding in older women; the latter becomes more strongly associated with ENC as the time from onset of menopause increases. Women with any of these risk factors as well as those who have taken estrogens for a long period of time should be screened for ENC at regular intervals. (14 refs)

79-6125 Malignant Tumors of the Vulva and Vagina. (Ger) Almendral, A. C. (Universitäts-Frauenklinik, Kantonsspital Basel, CH-4031 Basel, Switzerland); Torhorst, J. *Ther Umsch* 36(6): 538-545; 1979.

The literature concerning malignant tumors of the vulva and vagina is reviewed. Ninety-five percent of all malignant tumors of the vulva are primary, although metastases from primary endometrial, large intestinal, and uterine cervical carcinomas and from renal cell carcinoma, chorio-epithelioma, and vaginal tumors have been encountered. Squamous epithelial carcinoma accounts for 85% of all tumors of the vulva, malignant melanoma for 5%, basal cell carcinoma for 1%, and sarcoma for 2%. Vulval carcinoma develops mostly in the menopause; the av age of the patients is 65 yr, and the median age is 60 yr. The incidence is increased in single and nulliparous women. Chronic and nonspecific infections can be considered to be predisposing factors. Relationships between vulval carcinoma and syphilis, chronic granulomatosis, vulvitis, lymphogranuloma venereum, and condyloma acuminatum apparently exist. Herpes simplex virus type 2 may play an etiological role in vulval carcinoma. Invasive carcinoma is believed to develop from preexisting epithelial atypia. Malignant vaginal tumors account for 1.5-2% of all malignant tumors of the female genitalia. Squamous epithelial carcinoma accounts for about 93%, adenocarcinoma for 4%, and sarcoma for 1.6% of all primary vaginal tumors. The incidence of metastatic tumors, originating from tumors of the ovaries, uterus, vulva, rectum, and urinary bladder, is about twice as high as that of primary malignant tumors. The etiology of squamous epithelial carcinoma

is unknown, but the epidemiological factors involved may be similar to those in vulval carcinoma. The av age of patients with malignant vaginal tumors is 60 yr. Sarcoma botryoides occur mostly in children, while adenocarcinoma occurs mostly in young women after intrauterine exposure to diethylstilbestrol. (23 refs)

79-6126 Smoking and Health. (Ger) Grosser, P. J. (Hygiene-Institut des Bereichs Medizin (Charite), Humboldt-Universitat zu Berlin, Otto-Grotewohl-Strasse 1, DDR-108 Berlin, E. Germany). *Dtsch Gesundheitswes* 34(31): 1478-1481; 1979.

The physiological effects of smoking and its effect on life expectancy and incidence of disease (eg, chronic bronchitis, emphysema, cancer) are reviewed and discussed. Increased incidences of cancer of the larynx, oral cavity, esophagus, urinary bladder, kidneys, and pancreas are associated with the use of tobacco, in addition to the well-established increase in lung cancer incidence. (1 ref)

79-6127 The Epidemiology of Burkitt's Lymphoma: Evidence for a Causal Association with Epstein-Barr Virus. (Eng) de-The, G. (Centre National de le Recherche Scientifique, Univ. Lyon, Faculty Medicine Alexis Carrel, Lyon, France). *Epidemiol Rev (Baltimore)* 1: 32-54; 1979.

Epidemiologic evidence for an etiologic association between Epstein-Barr virus (EBV) and Burkitt's lymphoma (BL) is reviewed. The incidence of BL in Africa varies with altitude, av rainfall, av temperature, age, and sex, and shows some seasonal variation. An international research team in Uganda has established a causal association between high antibody titers to EBV and the risk of developing BL. Together with previous findings, these data indicate that EBV, under extreme conditions, has an oncogenic potential in humans. BL also seems to occur much more frequently in areas where malaria is endemic. A third factor, the presence of chromosomal anomalies, has been associated with the occurrence of BL as well as non-Burkitt's lymphomas. The origin of these chromosomal anomalies has not been determined. (94 refs)

CHEMICAL CARCINOGENESIS

- 79-6128 A Simple Theoretical Criterion of Chemical Carcinogenicity? (Eng) Herrmann, E. C. (Res. Lab., Schering AG, Mullerstrasse 178, D-1000 Berlin 65, W. Germany). *Experientia* 35(9): 1263-1264; 1979.

The simple theoretical criterion for chemical carcinogenicity based on the "average quasi-valence number" is discussed. Since the equation upon which this concept is based depends solely on the molecular formula, it suggests that all isomers of a given organic compound must have the same carcinogenic potential, which is not true. The possibility that carcinogenic metabolites may be formed from a given compound is also overlooked, as it is claimed that it is sufficient to inspect only the parent compound for carcinogenicity. There are also serious logical shortcomings inherent in this criterion. It has been suggested that as an additional necessary criterion for carcinogenicity, the existence of at least one UV-absorption peak in the "purely empirical" range of 206-248 nm must be demonstrated. However, it would be difficult in practice to predict the carcinogenicity of organic molecules by this improved method at a better than 1:1 chance. There are far better theoretical and experimental methods reported in the literature for identifying carcinogenic compounds. (7 refs)

- 79-6129 Serum-induced Chromosome Damage and Neoplastic Transformation of Mouse Cells In Vitro. (Eng) Sanford, K. K. (Lab. Cellular and Molecular Biology, NC1, Bethesda, MD 20014); Parshad, R.; Handelman, S. L.; Price, F. M.; Gantt, R. R.; Evans, V. J. *In Vitro* 15(7): 488-496; 1979.

Cells derived from C3H₁/HeN mouse embryos were grown in medium NCTC-135 supplemented with various combinations of large- and small-molecule fractions of horse serum (HS) and fetal bovine serum (FBS) in an effort to determine whether the small-molecule fraction of HS reproducibly accelerates neoplastic transformation and chromosomal damage, and whether the large-molecule fraction of FBS or of more serum prevents transformation and karyotypic alteration. In addition, an attempt was made to correlate cytologic changes with malignant transformation as tested by growth of cells as sarcomas in vivo. The large-molecule fraction of HS (mare or stallion) produced alterations in chromosome number and structure. HS also caused chromatid breaks and exchanges at or near the centromere; this is in contrast to fluorescent-light-induced breaks, which occur randomly along the chromatid. Efforts to control completely chromosome stability and malignant transformation through the use of large- and small-molecule fractions of HS and FBS or combinations thereof were unsuccessful. The results of in vivo assays indicated that the occurrence of neoplastic transformation cannot be correlated with any one serum fraction or combinations. Using a direct sampling method based on previously described cytologic criteria, diagnosis of malignant transformation was made in 11 cell lines; with one exception, the diagnoses were consistent with results of in vivo assays. (28 refs)

- 79-6130 Evaluation of Feasibility of Mutagenic Testing of Shale Oil Products and Effluents. (Eng) Epler, J. L.

(Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Rao, T. K.; Guerin, M. R. *Environ Health Perspect* 30: 179-184; 1979.

The Ames *Salmonella* histidine-reversion system was used to assay the mutagenic potential of crude shale oil, natural crude oil, and the product water from a shale oil process. Metabolic activation was provided with the use of liver homogenates from Aroclor 1254-induced rats. Preliminary results implicate chemicals occurring in the basic (ether-soluble) and neutral fractions as potential genetic hazards. Chemical constituents of these fractions (identified or predicted) were tested individually for mutagenicity, and the results were correlated with those of genetic monitoring. (17 refs)

- 79-6131 Chlorophyll: The Active Factor in Wheat Sprout Extract Inhibiting the Metabolic Activation of Carcinogens In Vitro. (Eng) Lai, C. N. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030). *Nutr Cancer* 1(3): 19-21; 1979.

The active factor in wheat sprout extract that inhibits the metabolic activation of carcinogens in vitro was studied. The inhibitory activities of wheat sprout extracts were directly correlated with chlorophyll levels. Root extract exhibited the same activity as leaf extract when compared at the same chlorophyll level. Chlorophyllin and chlorophyll extracted from wheat sprout chloroplasts did not affect the viability of cells in minimal glucose or nutrient agar plates. In liquid incubation, chlorophyllin reduced the growth of *Salmonella typhimurium* strain TA100 by half at a concentration of 0.6 mg/ml. Chlorophyll reduced the toxicity of several carcinogens, especially those not requiring liver S9 mix activation. Vitamin E and carotene showed little activity in the bacterial mutagenesis test. The potential of chlorophyll as a non-toxic chemopreventive agent appears promising. (8 refs)

- 79-6132 Arsenically Associated Cutaneous Squamous Cell Carcinoma with Hypercalcemia. (Eng) Southwick, G. J. (Dept. Head and Neck Surgery, Roswell Park Memorial Inst., Buffalo, NY); Schwartz, R. A. *J Surg Oncol* 12(2): 115-118; 1979.

The occurrence of an extensive squamous cell carcinoma complicated by hypercalcemia in a 62-yr-old white man who had been treated with 1% potassium arsenite for several years for psoriasis is reported. Steroid therapy had resulted in genital atrophy and bilateral cataract formation. Biopsy of an extensive ulcerative lesion of the right groin revealed well differentiated squamous cell carcinoma. Culture of material from the lesion revealed *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Two wk after hospitalization, the patient developed hypercalcemia (serum calcium, 14.2%), and he died 32 days after admission. Postmortem examination confirmed extensive squamous cell carcinoma of the right groin with local iliac bone invasion and lung metastasis. Extensive bilateral pulmonary atelectasis was also found. (5 refs)

- 79-6133 Asbestos-associated Neoplasms of B Cell Lineage. (Eng) Kagan, E. (Dept. Pathology, Georgetown Univ. Schs. Medicine and Dentistry, 3900 Reservoir Road, N. W., Washington, DC 20007); Jacobson, R. J.; Yeung, K. Y.; Haidak, D. J.; Nachnani, G. H. *Am J Med* 67(2): 325-330; 1979.

Three different asbestos-associated neoplasms of B-cell lineage, chronic lymphocytic leukemia, IgA myeloma, and IgG myeloma, were detected in three men (aged 54, 61, and 71 yr) who had heavy occupational exposure to asbestos dust. Two of the patients had coexistent pulmonary asbestosis, whereas the third patient had a pleural mesothelioma subsequent to his initial presentation with myeloma. Defective cell-mediated immunity and hyperactivity of B-cell function have previously been noted in patients with asbestosis. These asbestos-related immunologic derangements may predispose to the development of immunoproliferative and lymphoproliferative neoplasms, since these tumors have been observed in a variety of other settings characterized by protracted hyperactivity of the immune system. (27 refs)

- 79-6134 Binding of Beryllium to Nuclear Acidic Proteins. (Eng) Parker, V. H. (Molecular Toxicology Section, MRC Toxicology Unit, Medical Res. Council Labs., Woodmansterne Road, Carshalton, Surrey SM5 4EF, England); Stevens, C. *Chem Biol Interact* 26(2): 167-177; 1979.

To gain insight into the mechanism of beryllium toxicity, the in vitro binding of Be to rat liver nuclei was reassessed [$K_{As} = 2.0 \times 10^6$ M: n (binding sites) = 17 nanomoles(nmol) Be/mg protein]. Be also binds to rat liver nucleoli (K_{As} approx 4×10^6 M: $n = 10$ nmol Be/mg protein). Examination of rat liver chromatin fractionated on a hydroxyapatite column shows that Be does not bind to histone or to the nonhistone protein eluted by 0.05 M sodium phosphate. Be is strongly bound to the nonhistone proteins eluted by 0.2 M sodium phosphate ($K_{As} = 1.1 \times 10^6$ M: $n = 55$ nmol Be/mg protein) and, to the same extent, to the fraction containing DNA that is subsequently eluted from the column. Evidence is provided that the latter binding is not due to DNA. The fractions containing the Be-binding proteins also contain the proteins that are phosphorylated to the greater extent. (28 refs)

- 79-6135 Mutagenic Effects of Cadmium on Mammalian Oocyte Chromosomes. (Eng) Watanabe, T. (Dept. Hygiene and Preventive Medicine, Yamagata Univ. Sch. Medicine, Yamagata 990-23, Japan); Shimada, T.; Endo, A. *Mutat Res* 67(4): 349-356; 1979.

The mutagenic effects of cadmium chloride (1.0, 2.0, or 4.0 mg/kg, sc 5 hr before ovulation) on the metaphase-II oocyte chromosomes of virgin female golden hamsters were studied. No structural anomalies were observed, but the frequencies of hyperhaploidy and diploidy increased in the cadmium-treated hamsters, especially those given the higher doses. There were seven anaphase-I oocytes among the 536 oocytes examined. In one of these oocytes, one haploid set had 21 chromosomes and the other set had 23. Most of the increases in numerical anomalies were significant when compared with the results from control hamsters. No specific groups of chromosomes were affected. Oogenesis in the hamster appears to be much more sensitive to cadmium-induced chromosomal anomalies than does the same stage in the mouse. Severe and diffuse hemorrhage was observed on the ovaries of all hamsters given 2.0 or 4.0 mg/kg cadmium. Twelve hours after cadmium administration, 1.8, 2.3, and 3.7 $\mu\text{g/g}$ cad-

mium was found in the ovaries of the hamsters given 1.0, and 2.0, and 4.0 mg/kg cadmium chloride, respectively. Chromosome analysis of metaphase-II oocytes seems to be a useful method for screening the mutagenicity of environmental contaminants in mammalian germ cells in vivo. (31 refs)

- 79-6136 Cytotoxic and Clastogenic Effects of Soluble Chromium Compounds on Mammalian Cell Cultures. (Eng) Levis, A. G. (Inst. Animal Biology, Univ. Padua, Padua, Italy); Majone, F. *Br J Cancer* 40(4): 523-533; 1979.

Cell growth inhibition, reduction in cell survival and the induction of chromosome aberrations and sister chromatid exchange (SCE) were determined in cultured BHK and CHO hamster cell lines treated with 11 water-soluble hexavalent and trivalent chromium compounds. All Cr^{6+} compounds inhibited growth of BHK cells and reduced survival of CHO cells to levels comparable to those obtained only after exposure to Cr^{3+} concentrations 100- to 1,000-fold greater. The cytotoxicity curves obtained with the different Cr^{6+} compounds were almost overlapping, whereas marked differences of activity were found among Cr^{3+} compounds. Giant cells obtained after exposure to Cr^{6+} and Cr^{3+} compounds, as shown by the rise of DNA and RNA per cell, were due to the blockage of the cell cycle without sudden inhibition of macromolecular syntheses. While both Cr^{6+} and Cr^{3+} compounds were able to induce chromosome aberrations, only Cr^{6+} was active in inducing SCE, Cr^{3+} being absolutely incapable of doing so. The frequency of chromosome aberrations was increased about 10-fold after exposure to 1.0 $\mu\text{g/ml}$ Cr^{6+} , but only doubled after treatment with up to 150 $\mu\text{g/ml}$ Cr^{3+} . In spite of the sensitivity of CHO cells to the induction of SCE by mitomycin C, the frequency of SCE hardly doubled after exposure to Cr^{6+} compounds. The present data confirm that Cr^{6+} compounds are characterized by a marked cytotoxicity and clastogenic action on mammalian cell cultures and show that Cr^{3+} compounds, though cytotoxic only at extremely high concentrations and unable to increase the frequency of SCE, are not completely without cytogenetic effect. (35 refs)

- 79-6137 DNA Damage and DNA Repair in Cultured Human Cells Exposed to Chromate. (Eng) Whiting, R. F. (Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 West 10th Ave, Vancouver V5Z 1L3, Canada); Stich, H. F.; Koropatnick, D. J. *Chem Biol Interact* 26(3): 267-280; 1979.

DNA damage and DNA repair have been observed in cultured human skin fibroblasts exposed to potassium chromate but not to a chromic glycine complex. DNA repair synthesis (unscheduled incorporation of [^3H]thymidine) measured in cells during or following exposure to chromate was significant for chromate concentrations above 10^{-6} M. Maximal DNA repair was observed at about 10^{-4} M chromate; DNA repair capacity was saturated at this concentration. Chromate was stable for at least 8 hr in culture medium and produced approx a linear increase in repair with duration of exposure. DNA damage as determined by alkaline sucrose gradient sedimentation was detected after treatment for 1.5 hr with 5×10^{-4} M chromate. Exposure to 10^{-7} M chromate solution for 7 days inhibited colony formation while acute (1 hr) treatment was toxic at 5×10^{-6} M. The chromic glycine complex was toxic above 10^{-3} M for a 1-wk exposure but was not observably toxic after a 1-hr treatment. These results indicate that chromate rather than chromic compounds may be the carcinogenic form of the metal in humans. The nature of the ultimate carcinogen is discussed. (17 refs)

- 79-6138 Sister Chromatid Exchanges Induced in Cultured Mammalian Cells by Chromate. (Eng) Macrae, W. D. (Environmental Carcinogenesis Unit, British Columbia Cancer Res. Center 601, W. 10th Ave., Vancouver V5Z 1L3, British Columbia, Canada); Whiting, R. F.; Stich, H. F. *Chem Biol Interact* 26(3): 281-286; 1979.

The ability of chromate compounds to induce sister chromatid exchanges (SCEs) and chromosome aberrations in human fibroblasts and Chinese hamster ovary (CHO) cells was studied. Chromate compounds at low concentrations induced SCEs and chromosome aberrations in cultured human cells and SCEs in CHO cells. SCE frequency was increased about fourfold over the spontaneous level in human fibroblasts exposed to 10^{-6} M $K_2Cr_2O_7$ or K_2CrO_4 for 48 hr. Chromosome aberrations (primarily chromatid breaks) were also produced in human cells exposed to K_2CrO_4 at concentrations between 8×10^{-7} and 3×10^{-6} M. K_2CrO_4 , but not the trivalent compound $CrCl_3$, induced SCEs in CHO cells at the concentrations tested (10^{-7} - 10^{-5} M); the max SCE level represented a threefold increase over the spontaneous level. The results support the view that chromate compounds may possess mutagenic or carcinogenic activity. (12 refs)

- 79-6139 Establishment of Photoaffinity Label Derivatives of Fluorene as Probes in Studies of Chemical Carcinogenesis in Mammalian Cell Culture. (Eng) Sarraf, A. M. (PO Box 191, Dept. Pharmacology, Univ. Alabama in Birmingham Medical Center, Birmingham, AL 35294); White, W. E.; DiVito, N. *Cancer Res* 39(10): 3903-3908; 1979.

The ability of several bifunctional azidofluorenes (photosensitive analogs of the carcinogen 2-acetylaminofluorene) to transform mouse embryo C3H 10T1/2 cells under conditions of photolysis in situ was studied. Under the conditions studied, UV light was neither toxic nor transforming. The cytotoxic effects of 2,5-diazidofluorene (2,5-DAzF), 2,7-diazidofluorene (2,7-DAzF), and 2-azidofluorene (2-AzF) were identical when the cells were incubated with the drugs in the dark or when the drugs were irradiated in phosphate-buffered saline (PBS) and then added to the cells. When the drugs were added to the cells and then irradiated for ≥ 15 min in complete medium (CM), the cytotoxicities of 2,5-DAzF and 2,7-DAzF were severalfold higher than those of 2-AzF and 7-bromo-2-azidofluorene. The transformation frequency obtained with $1 \mu\text{g/ml}$ 2,5-DAzF or 2,7-DAzF in CM was 4.8 transformed foci/1,000 surviving cells. At $2 \mu\text{g/ml}$, UV irradiation in CM for 15 sec led to transformation by both drugs. 2-DAzF appeared to exert no action on the effect of UV. Preirradiated azidofluorene derivatives were only very weakly transforming for 10T1/2 cells, forming only type II foci. (23 refs)

- 79-6140 Chromosome Breaking Activity of Human Feces and Its Enhancement by Transition Metals. (Eng) Stich, H. F. (Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 W. 10th Avenue, Vancouver, B.C., V5Z 1L3, Canada); Kuhnlein, U. *Int J Cancer* 24(3): 284-287; 1979.

Chloroform-methanol extracts of feces collected from three apparently healthy persons were tested for their ability to induce chromosome aberrations in cultured Chinese hamster ovary (CHO) cells. The CHO cells were exposed for 3 hr under aerobic conditions to fecal extract diluted in the range 1:10 to 1:320 in culture medium. The frequency of plates with well-defined chromosome aberrations, including breaks, acentric fragments,

and exchanges, significantly increased following exposure to the fecal extracts. The addition of manganese (Mn^{2+} ; 10^{-4} M) and, to a lesser degree, of copper (Cu^{2+} ; 10^{-5} M) stimulated the induction of chromosome aberrations, while iron (Fe^{2+} and Fe^{3+} ; both 10^{-4} M) inhibited it. The effects on mitotic inhibition were similar. The addition of catalase to the fecal extract or to the mixture of fecal extract and Mn^{2+} abolished the mitotic inhibition and greatly reduced the frequency of chromosome aberrations. It is suggested that the capacity of fecal extracts to induce chromosome aberrations might play a role in the etiology of colon cancer. (17 refs)

- 79-6141 Enhancement by Transition Metals of Unscheduled DNA Synthesis Induced by Isoniazid and Related Hydrazines in Cultured Normal and Xeroderma Pigmentosum Human Cells. (Eng) Whiting, R. F. (Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, Vancouver, B. C., Canada); Wei, L.; Stich, H. F. *Mutat Res* 62(3): 505-515; 1979.

In combination with the transition metals $Mn(II)$, $Cu(II)$, and $Fe(III)$, isoniazid and related hydrazine compounds induced unscheduled DNA synthesis (DNA repair) in cultured human fibroblasts. Manganese at 10^{-5} and 10^{-4} M strongly enhanced DNA repair induced by isoniazid, iproniazid, nialamide, and hydrazine. Peak levels of DNA repair occurred at 5×10^{-4} - 10^{-3} M of the four hydrazine compounds. Copper caused less enhancement of DNA repair, while iron had no detectable effect. Without added metal, unscheduled DNA synthesis was not observed in cells treated with any of the freshly-prepared hydrazine compounds. However, following preincubation in medium for 6-12 hr, isoniazid alone at high concentrations (10^{-2} - 10^{-1} M) induced DNA repair. With isoniazid/manganese mixtures, preincubation did not further enhance DNA repair except at low concentrations of isoniazid (2.5×10^{-4} M). Catalase reduced the DNA damage caused by preincubated isoniazid and by the isoniazid/metal mixtures. Exposure of repair-deficient xeroderma pigmentosum cells to isoniazid plus manganese resulted in a DNA-repair profile similar to that of normal cells. The results are consistent with the assumption that hydrogen peroxide is a critical intermediate for the production of free radicals that cause the observed DNA damage. (24 refs)

- 79-6142 Fate of Nickel Subsulfide During Carcinogenesis Studied by Autoradiography and X-Ray Powder Diffraction. (Eng) Oskarsson, A. (Dept. Toxicology, Univ. Uppsala, Uppsala, Sweden); Andersson, Y.; Tjalve, H. *Cancer Res* 39(10): 4175-4182; 1979.

Sarcomas were induced in mice by the im and sc administration of ^{63}Ni - and ^{35}S -labeled nickel subsulfide, and the fate of the Ni_3S_2 during carcinogenesis was studied. Whole-body autoradiography showed a gradual loss of solubilized ^{63}Ni and ^{35}S radioactivity from the injection site. There was also a loss of nonsolubilized dust particles, which appeared to be phagocytized by reticuloendothelial cells in the liver, spleen, and regional lymph nodes. Microautoradiography showed that the radioactivity within both the $^{63}Ni_3S_2$ - and the $Ni_3^{35}S_2$ -induced tumors was associated almost exclusively with dust particles. There was no specific or excessive localization of solubilized radioactivity in the tumors or in metastases. Two patterns of localization of dust particles within the tumors were observed: one with particles concentrated in a central part of the tumor and one with the particles present in the periphery of the tumor. X-ray powder diffraction of the insoluble crystalline material in the tumors indicated that conversion of αNi_3S_2 to αNi_7S_6 and βNiS had occurred. (20 refs)

- 79-6143 Mutagenic Activity of Anticancer Agent *cis*-Dichlorodiammine Platinum-II. (Eng) Wiencke, J. K. (Dept. Environmental Health, Univ. Minnesota, Sch. Public Health, Minneapolis, MN 55455); Cervenka, J.; Paulus, H. *Mutat Res* 68(1): 69-77; 1979.

cis-Dichlorodiamminoplatinum-II (*cis*-DDP) has been widely used as an anticancer chemotherapeutic agent. The mutagenicity of *cis*-DDP was investigated in vitro and in vivo by measuring sister-chromatid exchange (SCE) and chromosomal aberrations. Parallel human lymphocyte cultures were incubated with and without the addition of bromodeoxyuridine (BrdU) at four concentrations of *cis*-DDP [0.25, 0.50, 0.75, and 1.00 μ g/ml]. Significant increases in SCE rate were observed at 0.25 μ g/ml and higher, showing a clear dose response relationship between SCE rate and *cis*-DDP concentration. A significant increase in chromosome breakage and tetradial figures was observed in BrdU-free cultures treated with *cis*-DDP, again showing a dose dependency. Analysis of the distribution of cells in the first, second and third division in *cis*-DDP-treated cultures demonstrated that the drug depressed mitotic activity. In vivo analysis of SCE and chromosome aberrations in mice showed that 13.85 mg/kg ip of *cis*-DDP produced significant increases in the rate of SCE and chromosome aberrations in bone-marrow cells. (34 refs)

- 79-6144 In Vivo Conversion of Sodium Azide to a Stable Mutagenic Metabolite in *Salmonella typhimurium*. (Eng) Owais, W. M. (Program in Genetics, Washington State Univ., Pullman, WA 99164); Kleinhofs, A.; Nilan, R. A. *Mutat Res* 68(1): 15-22; 1979.

Salmonella typhimurium strains TA1530 and G46 growing in the presence of 5×10^{-4} M sodium azide produced a mutagenic metabolite, most of which was found in the growth medium. The metabolite was highly mutagenic in the base-substitution strains TA1530 and TA1535 but not in the frameshift mutants TA1537 and TA1538. Metabolite production in TA1530 occurred in the log phase of bacterial growth between 2-12 hr in the growth cycle. In G46, metabolite production also occurred in log phase between 2-8 hr in the growing cycle. Unlike azide, the metabolite induced mutations in resting TA1530 strain cells at pH 6 and 9. Neither the metabolite nor azide reverted resting cells of the G46 strain. The ability of cells to produce a mutagenic metabolite from azide may represent a new dangerous aspect of environmental mutagenesis. (28 refs)

- 79-6145 Simultaneous Staining of Sister Chromatid Exchanges and Q-Bands in Human Chromosomes After Treatment with Methyl Methane Sulphonate, Quinacrine Mustard, and Quinacrine. (Eng) Haglund, U. (Dept. Medical Cell Genetics, Medical Nobel Inst., Karolinska Institutet, S-10401 Stockholm 60, Sweden); Zech, L. *Hum Genet* 49(3): 307-317; 1979.

A method for staining bromodeoxyuridine (BrdU)-treated human peripheral blood lymphocytes using only quinacrine mustard (QM) was developed, and sister-chromatid exchanges (SCE's) and the Q-banding patterns of the stained cells were examined. The number of SCE's per chromosome was in good agreement with the Poisson distribution. In all but one group of cells treated with methyl methanesulfonate (MMS), QM, or quinacrine (Q), there was an increase in SCE frequency ($p < 0.01$). The longer chromosomes (A-C) tended to show more SCE's than expected, and the short ones (D-G) tended to show fewer than expected. When groups treated

with QM and Q, respectively, were pooled, a significant difference was found between long and short chromosomes in SCE frequency compared with that in MMS-treated cells. The greatest proportion of SCE's (76%) was located on the pale chromosome bands; 13% were located on the intense Q bands, and 11% were located at junction areas. None of the chemicals used altered the pattern of occurrence of SCE's. In a number of cases, SCE's appeared to occur at identical sites in homologous chromosomes. The number of SCE's occurring at identical sites exceeded the number expected ($p < 0.001$). Only a few structural aberrations were found, and there were fewer in the treated cells than in the untreated control cells. (24 refs)

- 79-6146 Mutagenicity of the Naturally Occurring Carcinogen Cycasin and Synthetic Methylazoxymethanol Conjugates in *Salmonella typhimurium*. (Eng) Matsushima, T. (Dept. Molecular Oncology, Inst. Medical Science, Univ. Tokyo, Shirokane-dai, Minato-ku, Tokyo 108, Japan); Matsumoto, H.; Shirai, A.; Sawamura, M.; Sugimura, T. *Cancer Res* 39(9): 3780-3782; 1979.

The mutagenicity of cycasin was demonstrated in a modification of the Ames *Salmonella* test in which the compound was preincubated with β -glucosidase and the tester strain in liquid medium. The mutagenicity of cycasin to six histidine-dependent *Salmonella* strains varied considerably, with strain HisG46 being the most susceptible. Methylazoxymethyl- β -D-glucosiduronic acid, which also has been considered nonmutagenic, similarly became mutagenic when preincubated with β -glucuronidase. Methylazoxymethyl acetate, which is slightly mutagenic in the Ames standard pour plate assay, became highly mutagenic upon preincubation. The mutagenicity of free methylazoxymethanol was confirmed, and a linear dose-response relationship was observed. The common conditions required for the activation of nonmutagenic methylazoxymethanol conjugates, cycasin, and methylazoxymethyl- β -D-glucosiduronic acid are a 90-min preincubation at 30 C, pH 6.5, with an appropriate hydrolase and *Salmonella typhimurium* HisG46. (18 refs)

- 79-6147 Methanol Potentiation of Carbon Tetrachloride-induced Hepatotoxicity. (Eng) Cantilena, L. R. (Dept. Pharmacology, Univ. Kansas Medical Center, Coll. Health Sciences and Hosp., Kansas City, KS 66103); Cagen, S. Z.; Klaassen, C. D. *Proc Soc Exp Biol Med* 162(1): 90-95; 1979.

The mechanism by which methanol (M) and other aliphatic alcohols potentiate carbon tetrachloride hepatotoxicity was investigated in Sprague-Dawley rats. M administration (7 ml/kg, po) was followed at various times by CCl_4 administration (0.1 ml/kg, ip). Max potentiation of serum alanine aminotransferase (ALT) by M occurred when CCl_4 was administered 48 hr after M administration. However, all subsequent observations were made 24 hr after M administration, since individual variation was greatest at 48 hr. Pretreatment 24 hr before CCl_4 administration with M or isopropanol (2.5 ml/kg, po), but not ethanol (6 ml/kg, po), elevated plasma ALT activity and hepatic triglyceride levels and decreased hepatic glucose-6-phosphatase activity relative to that in animals receiving only CCl_4 (0.01-0.3 ml/kg, ip). CCl_4 administration alone (0.1 ml/kg, ip) or after M pretreatment did not enhance lipid peroxidation in vivo, as determined by diene conjugation. M Pretreatment did enhance the covalent binding of Cl_4 -labeled CCl_4 to isolated microsomal protein and microsomal lipid. M alone caused significant alterations in hepatic triglyceride and glucose-6-

phosphatase levels but not plasma ALT activity, although the effect of M plus CCl₄ on plasma ALT was greater than the additive. It is concluded that M and isopropanol both potentiate CCl₄ hepatotoxicity by increasing the covalent binding of the compound to microsomal proteins and lipids. (23 refs)

- 79-6148 Metabolism of the Colon Carcinogen Methylazoxymethanol Acetate. (Eng) Zedeck, M. S. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Frank, N.; Wiessler, M. *Front Gastrointest Res* 4: 32-37; 1979.

The metabolism of the colon carcinogen methylazoxymethanol acetate (MAM, 10 ml/kg, ip or iv) by male Sprague-Dawley rats was compared with that of acetoxymethyl-methyl-N-nitrosamine (AMMN) and N-methyl-N-nitrosourea (MNU). The rats were pretreated with pyrazole (180 mg/kg) or disulfiram (1 g/kg). The lethal effects of MAM were potentiated by prior treatment with disulfiram, but blocked by pyrazole pretreatment. The lethal effects of AMMN and MNU were not affected by prior treatment with pyrazole. MAM (10 mg/kg) inhibited thymidine incorporation into DNA by approx 15%, and pretreatment with disulfiram resulted in 65% inhibition. Histologic abnormalities in the colonic epithelium were increased in disulfiram-pretreated animals. Pyrazole pretreatment significantly reduced the MAM-induced inhibition of thymidine incorporation into colonic DNA. Pyrazole also eliminated the histologic abnormalities in the colonic epithelium seen after MAM. The results suggest that the metabolite of MAM responsible for its toxicity is probably the corresponding aldehyde. (11 refs)

- 79-6149 Formation of Carbonyl Chloride in Carbon Tetrachloride Metabolism by Rat Liver In Vitro. (Eng) Shah, H. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Hartman, S. P.; Weinhouse, S. *Cancer Res* 39(10): 3942-3947; 1979.

To identify intermediates of carbon tetrachloride metabolism, whole, suitably fortified rat liver homogenates were incubated with ¹⁴CCl₄ in the presence and absence of pools of unlabeled, suspected intermediates. In the presence of NADH or NADPH, incorporation of radioactivity was rapid and substantial in CO₂, lipid, protein, and the acid-soluble fraction. It was not influenced by the presence of large pools of unlabeled chloroform or formate, thus excluding these substances as obligatory intermediates. However, when incubated with L-cysteine, incorporation of radioactivity in the acid-soluble fraction was almost doubled, and about one-third of the radioactivity of this fraction was identified as 2-oxothiazolidine 4-carboxylic acid. Based on current knowledge of CCl₄ metabolism, the following aerobic pathway is proposed: microsomal cleavage to Cl⁻ and ·CCl₃ and oxidation of the latter to the unstable intermediate, Cl₃COH, which loses HCl to yield COCl₂. COCl₂ is likely to be the major source of CO₂ from CCl₄, but is probably not the intermediate that binds to lipid and protein. The addition of glutathione had no effect on CCl₄ metabolism in rat liver homogenate, suggesting that glutathione S-transferases, which catalyze other dehalogenation reactions, do not play a role in CCl₄ metabolism. (35 refs)

- 79-6150 Binding of Carcinogenic Halogenated Hydrocarbons to Cell Macromolecules. (Eng) Banerjee, S. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental

Medicine, New York Univ. Medical Center, New York, NY 10016); Van Duuren, B. L. *J Natl Cancer Inst* 63(3): 707-711; 1979.

Liver and stomach microsomal preparations obtained from 7- to 10-wk-old B6C3F₁ mice were incubated individually with [¹⁴C]ethylene dibromide (EDB), or [¹⁴C]ethylene dichloride (EDC), salmon sperm DNA, and an NADPH-generating system at 37 C for 60 min. Both EDB and EDC bound to stomach and hepatic microsomal proteins and to salmon sperm DNA. The binding of EDB to protein of denatured stomach microsomes was 4% compared to that obtained with native microsomes. Only 1% of EDB that was bound to hepatic protein in the presence of intact microsomes was bound in the presence of denatured hepatic microsomes. The amount of EDB bound to protein or to DNA increased with greater concentrations of hepatic or gastric microsomes. SKF-525A, an inhibitor of the microsomal metabolism of various substrates, significantly inhibited the binding of EDB to protein and DNA; binding of EDB to hepatic microsomal protein was inhibited by 79%. Glutathione and 1-methyl-2-mercaptoimidazole markedly decreased the binding of EDB, which indicated that a reactive electrophilic intermediate of EDB is involved in the binding. The binding of EDC to liver proteins of (C57BL/6x3H/H3)F₁ mice, which are susceptible to liver tumor induction by EDC and to DNA, was significantly higher than the corresponding binding for Osborne-Mendel rats, a species not susceptible to liver tumor induction by this compound. These results suggest that metabolic activation of EDB and EDC is required for their covalent binding to macromolecules. (26 refs)

- 79-6151 Metabolic Activation of Chlorinated Ethylene Derivatives. (Eng) Henschler, D. (Inst. Toxicology, Univ. Wurzburg, D-8700 Wurzburg, W. Germany); Bonse, G. *Adv Pharmacol Ther* 9: 123-130; 1979.

The chlorinated ethylenes (CE), were studied to determine the structural requirements for their oncogenic effects. The epoxides of all CEs except 1,1-dichloroethylene oxide were prepared, and the in vitro rearrangement mechanisms were studied. The epoxide rearrangement products were either chlorinated aldehydes or acyl chlorides. The metabolites excreted in vivo, chlorinated ethanols and acetic acids, can be derived from these epoxide rearrangement products. Trichloroethylene was an exception; its epoxide rearranged in vitro to dichloroacetyl chloride, whereas the metabolites are oxidation or reduction products, respectively of trichloroacetaldehyde. In vivo, trichloroethylene epoxide is converted, via the trivalent iron of cytochrome P450, at the site of formation in the hydrophobic premise to chloral. In a modified Ames test system using *Escherichia coli* K 12, vinyl chloride, vinylidene chloride, and trichloroethylene exerted mutagenic activity after activation by induced liver microsomes. The tetra- and 1,2-dichloroethylenes (cis and trans) were inactive in this system. A molecular rule derived from these findings states that unsymmetric chlorine substitution induces, by an imbalanced electron withdrawing effect, the epoxides to become highly electrophilic, this being a prerequisite for mutagenicity and carcinogenicity. (18 refs)

- 79-6152 Spontaneous and Induced *rho* Mutants of *Saccharomyces cerevisiae*: Patterns of Loss of Mitochondrial Genetic Markers. (Eng) Heude, M. (Institut Curie-Biologie, Centre Universitaire, 91405 Orsay, France); Fukuhara, H.; Moustacchi, E. *J Bacteriol* 139(2): 460-467; 1979.

Fifteen mitochondrial genetic markers were examined in independent spontaneous *rho* mutants of *Saccharomyces cerevisiae* to determine whether any specific pattern of deletion could be observed. Among the 597 isolated *rho* clones in which the genotype was completely determined, only 2.5% retained the 15 markers; 6.2% lost all of the markers, and 7.4% were multiple deletions. The segment *oxi3-phol/O(II)-mit175*, alone or in association with other markers, was included in numerous types of deletions. When the loss frequency of each marker was plotted as a function of its position on the gene map, a progressive decline appeared on each side of the preferentially lost region, *oxi3-phol/O(II)-mit175*. Previously reported data concerning 3-carbethoxypsoralen- and ethidium bromide-induced *rho* mutants were compared with the pattern of spontaneous *rho* mutants; the sensitive region was the same in both cases. The regions flanking the sensitive region were lost much less often in induced than in spontaneous *rho* mutants, indicating a special sensitivity of the *oxi3-phol/O(II)-mit175* region to mutagenic agents. These results suggest that the basic mechanism of *rho* induction is the same in spontaneous and induced mutagenesis. (28 refs)

- 79-6153 Tumors in Male Rats Fed Ethyl Chlorophenoxyisobutyrate, a Hypolipidemic Drug. (Eng) Svoboda, D. J. (Dept. Pathology, Univ. Kansas, Coll. Health Sciences and Hosp., Kansas City, KS 66103); Azarnoff, D. L. *Cancer Res* 39(9): 3419-3428; 1979.

The tumorigenicity of the hypolipidemic drug clofibrate (ethyl chlorophenoxyisobutyrate, Atromid-S) was determined in male F344 rats. The drug was fed at a concentration of 0.5% in the diet of 25 rats for 72-97 wk, and the animals were inspected for tumors up to a max of 129 wk. Between 72 and 129 wk, there were 10 rats with a total of 16 tumors. These included four hepatocellular carcinomas, an adenocarcinoma of the glandular stomach, a papillary carcinoma of the urinary bladder, an acinar cell carcinoma of the pancreas, a lymphosarcoma involving the pancreas, acinar cell adenomas of the pancreas, a renal carcinoma, and sarcomas of the lung and parotid gland. Although the number of experimental animals was small, none of these tumors were present in 25 controls, and systematic examination of available literature dealing with spontaneous tumors in several thousand rats indicated that the tumors in clofibrate-fed rats were not spontaneous. Several of the tumors were transplanted through several generations. Clofibrate, like two other hypolipidemic drugs that are carcinogenic, causes peroxisome proliferation. It is speculated that some drugs that cause peroxisome proliferation may represent a new class of chemical carcinogens and that there may be a relationship between peroxisome proliferation and malignant transformation. (60 refs)

- 79-6154 Tumorigenicity of the Hypolipidaemic Peroxisome Proliferator Ethyl- α -p-chlorophenoxyisobutyrate (Clofibrate) in Rats. (Eng) Reddy, J. K. (Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL); Qureshi, S. A. *Br J Cancer* 40(3): 476-482; 1979.

Ethyl- α -p-chlorophenoxyisobutyrate (clofibrate), a hypolipidemic drug which induces hepatomegaly and peroxisome proliferation in rat and mouse liver cells, was fed to 15 male F344 rats at a dietary concentration of 0.5% for up to 28 mo. Hepatocellular carcinomas developed in 10/11 (91%) rats killed between 24 and 28 mo. Other tumors included two pancreatic carcinomas, a leiomyoma of the small intestine, and a large dermatofibrosar-

coma. Clofibrate is the third hypolipidemic peroxisome proliferator demonstrated to be hepatocarcinogenic in rats. These studies suggest that hypolipidemic agents which are capable of producing a sustained hepatomegaly and peroxisome-proliferative effect may also induce liver tumors. (29 refs)

- 79-6155 Application of Clofibrate in the 70s. Epidemiological Aspects. (Swe) Bergstrom, I. (Ostersund, Sweden); Boethius, G.; Rydstrom, P. O. *Lakartidningen* 76(28/29): 2538-2539; 1979.

One hundred and twenty-five persons (63 men and 62 women, aged >30 yr) for whom clofibrate was prescribed were followed up for possible side effects in an epidemiological study. Four patients (all women) developed malignant diseases during the observation period. In two of these patients, malignant diseases (not specified) were diagnosed 5 yr after the prescription of 100 and 200 capsules of Atromidin, respectively. Another patient developed breast cancer 1 yr after clofibrate treatment (3 prescriptions), and ovarian cancer was found in the fourth woman about 3 yr after 2 yr of clofibrate treatment. In view of the small number of the patients involved, it is impossible to evaluate the possible increase in cancer risk following clofibrate treatment. (5 refs)

- 79-6156 Effect of Carcinogen Ethionine on Enzymatic Methylation of DNA Sequences with Various Degrees of Repetitiveness. (Eng) Boehm, T. L. (Zentrum der Biologischen Chemie der Universitat Frankfurt am Main, Theodor-Stern Kai 7, D-6000 Frankfurt am Main 70, W. Germany); Drahovsky, D. *Eur J Cancer* 15(9): 1167-1173; 1979.

The effect of ethionine on the pattern of enzymatic DNA methylation in sequences of various functions and degrees of repetitiveness was studied in P815 mastocytoma cells. The cells were labeled simultaneously with [14 C]deoxycytidine and L-[methyl- 3 H]methionine. After 48 hr, DNA was isolated by repeated ribonuclease and pronase treatment and sonicated to a fragment length of about 450 base pairs. Separation of inverted (ABC...CBA) and ordinary repetitive ABC...ABC...ABC DNA sequences was achieved after heat denaturation and reassociation to $Cot < 0.001$. The individual fractions were hydrolyzed in 96% formic acid, and the DNA bases were separated by paper chromatography. The relative rates of enzymatic DNA methylation were computed and indicated that the inverted repetitive sequences were methylated 50% more than the ordinary repetitive sequences and about 300% more than the intermediary and unique sequences. These methylation rates changed dramatically in cells grown in the presence of ethionine. At an ethionine concentration as low as 0.01 mM, the methylation of inverted repetitive sequences dropped to the level of enzymatic methylation of the ordinary repetitive sequences and remained unchanged up to 0.3 mM. The other sequence classes were also less methylated in cells grown in the presence of ethionine, but the effect was less pronounced. The inverted repetitive sequences might represent acceptor sites for regulatory sites for regulatory protein, and their hypomethylation may be related to the ethionine-induced re-expression of certain genes. (42 refs)

- 79-6157 Metabolic Activation and Deactivation of Mutagens and Carcinogens. (Eng) De Flora, S. (Istituto di Igienologia, Università di Genova, Genoa, Italy). *Ital J Biochem* 28(2): 81-103; 1979.

The in vitro metabolic behavior of 14 mutagens was investigated in the Ames *Salmonella typhimurium* test in the presence and absence of a rat liver microsomal fraction (S-9 mix) and an NADPH-generating system. Dose-response curves were obtained by relating the amounts of mutagenic compounds to the number of TA100 revertants per plate induced in the absence or in the presence of S-9 mix. In the presence of S-9 2-aminofluorene and benzo(a)pyrene were activated, while there was a slight increase in the mutagenicity of 1,2-epoxybutane. Glycidol, folpet (N-trichloromethylthiophthalimide), nitrofurantoin, and 2-nitronaphthalene were all unchanged in the presence of S-9. The activities of 1,1,1-trichloropropene-2,3-oxide, sodium nitrite, sodium nitrites, 5-nitro-2-furoic acid, and captan (N-trichloromethylthiotetrahydrophthalimide) were decreased. Styrene oxide, sodium azide, and sodium dichromate were deactivated as mutagens in the presence of S-9. These metabolic variations of mutagenicity may account for at least a part of the conflicting nature of in vivo and in vitro findings. Some of the so-called false positives in the *Salmonella* test should be envisaged as true mutagens, which can undergo metabolic deactivation processes and yield negative results in animal carcinogenicity tests. These in vitro findings may be useful to explain the epidemiological data and the results of animal tests, and to assess the possible health hazards of mutagens. (40 refs)

- 79-6158 Mutagenicity of Chloroprene, 1-Chloro-1,3-*trans*-Butadiene, 1,4-Dichlorobutene-2 and 1,4-Dichloro-2,3-Epoxybutane in *Drosophila melanogaster*. (Eng) Vogel, E. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands). *Mutat Res* 67(4): 377-381; 1979.

The mutagenicity of the following halo-olefins for *Drosophila melanogaster* were studied: 2-chloro-1,3-butadiene (chloroprene), 1-chloro-1,3-butadiene (1-CB), 1,4-dichlorobutene-2 (DCB), and 1,4-dichloro-2,3-epoxybutane (DCEB). Chloroprene increased the percentage of recessive lethals ($P < 0.01$) in the *Basc* test, in which male Berlin K flies were fed the chemicals and mated to virgin females; the effect was not dose-related. A highly purified sample of chloroprene was noncytotoxic, but 40%-60% of treated males died within 66-72 hr after exposure to 11.4 mM of a sample containing several impurities. 1-CB was slightly more mutagenic than chloroprene, and DCB and DCEB proved to be both mutagenic and cytotoxic. These results confirm those obtained in other mutagenicity assay systems. (10 refs)

- 79-6159 Pleiotropic Effects of Ribosomal Mutations for Cycloheximide Resistance in a Double-resistant Homocaryon of *Neurospora crassa*. (Eng) Vomvovanni, V. E. (Dept. Biology, Nuclear Res. Center Democritos, Aghia Paraskevi, Athens, Greece); Argyrakakis, M. P. *J Bacteriol* 139(2): 620-624; 1979.

Pleiotropic effects of two ribosomal mutations for cycloheximide resistance were studied in an *act-2 act-3* double-resistant homocaryon (strain dm6596) of *Neurospora crassa*. Morphologically, the dm6596 strain had a compact and highly branched colony structure compared with the spreading filamentous form of the wild type and the two parental strains. In liquid shake cultures the rate of increase of the mycelial mass of the dm6596 strain was slowed to 50% of the rate of the wild type and the two parental strains; the mycelial front of dm6596 in Ryan tubes proceeded at $\leq 30\%$ of the wild-type rates. After sucrose density gra-

dient centrifugation, the 40S ribosomal subunits appeared to be in excess in dm6596, whereas they were present in a 1:1 ratio in the wild-type strains. Lowering the temperature from 30 C to 25 C resulted in a 70% decrease in the growth rate of dm6596 in Ryan tubes compared with a 20% decrease for the other strains. Growth in liquid media was not cold sensitive. It is suggested that the observed morphological alterations can be imposed by either translational discrimination of altered ribosomes for a given messenger RNA or lack of the ability of a given protein to be properly integrated into a functional unit in cell membranes modified after the attachment of mutated ribosomes. (16 refs)

- 79-6160 Mutagenicity of 1,2-Dicarbonyl Compounds: Maltol, Kojic Acid, Diacetyl and Related Substances. (Eng) Bjeldanes, L. F. (Dept. Nutritional Sciences, Univ. California, Berkeley, CA 94720); Chew, H. *Mutat Res* 67(4): 367-371; 1979.

The mutagenicity of maltol, kojic acid, diacetyl, and related substances in *Salmonella typhimurium* strains TA98 and TA100 was studied. Glyoxal, diacetyl, 1,2-cyclohexanedione, maltol, ethyl maltol, and kojic acid showed dose-related mutagenic activity in strain TA100, but not in strain TA98. S9 liver microsome preparation had little effect on the activity of these compounds. Dimethyl oxalate, pyruvic acid, ninhydrin, 3-methyl-1,2-cyclopentanedione, α -pyrone, chromone-2-carboxylic acid, 1,2-naphthoquinone, dehydroascorbic acid, and catechol had no mutagenic effect on either tester strain in the presence or absence of the S9 mix. 2-Hydroxy-1,4-naphthoquinone (>1 mg/plate) and 1,4-benzoquinone (>5 μ g/plate) were toxic but not mutagenic. Although the mutagenic activities of the environmentally important 1,2-dicarbonyl compounds must be classified as weak, detailed investigations into the genetic toxicology of some of these compounds are warranted. (19 refs)

- 79-6161 Enhancement of Artificial Lung Metastases in Mice Caused by Cyclophosphamide. I. Participation of Impairment of Host Antitumor Resistance. (Eng) Milas, L. (Labs. Immunology, Dept. Physiology, Medical Faculty, Central Inst. Tumors and Allied Diseases, Univ. Zagreb, Ilica 197, 41000 Zagreb, Yugoslavia); Malenica, B.; Allegretti, N. *Cancer Immunol Immunother* 6(3): 191-196; 1979.

The mechanism of cyclophosphamide (CY, 50-250 mg/kg, ip, 1 day before iv inoculation of 10^4 tumor cells)-enhancement of lung metastases was studied using CBA mice and the syngeneic FSa fibrosarcoma. CY markedly enhanced metastasis formation; the number of lung metastases increased with dose up to 180 mg/kg. The highest yield of metastases was obtained when tumor cells were injected 1 day after CY, the yield being almost nil in mice given CY 14 days before tumor inoculation. CY was also effective in increasing metastasis in whole body-irradiated and TIR mice. Its effect, however, was abolished to a great extent by reconstituting mice with nonseparated or nonadherent spleen and bone marrow cells from either normal or TIR mice. Lymphoid cells from CY-treated mice had no such reconstitutive capacity. The data suggest that CY-induced enhancement of tumor metastasis formation was partly due to nonimmunologic factors and partly due to suppression of non-T lymphocytes. (21 refs)

- 79-6162 A Comparison of Lithocholic Acid Metabolism by Intestinal Microflora in Subjects of High- and Low-Risk

Colon Cancer Populations. (Eng) Kelsey, M. I. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Molina, J. E.; Hwang, K. K. *Front Gastrointest Res* 4: 38-50; 1979.

The metabolism of lithocholic acid-3 α -sulfate (LASO₄) by the intestinal microflora of human volunteers consuming high-beef (high risk for contracting colon cancer), low-beef, or vegetarian (low risk for contracting colon cancer) diets was studied. Microflora obtained from an individual on a high-beef diet (HBD) metabolized tauroolithocholate (TL) to 5 β -cholanolic acid, 3-keto-cholanolic acid (3-keto), and a mixture of lithocholic acid (LA) and isolithocholic (ILA) acid. When LA was used as a substrate, the metabolites were ethyl LA, 3-keto, LA, and ILA and its sulfate ester. Metabolites of sulfolithocholic acid (LASO) were 5 β -cholanolic acid, LA, ILA, and an unsaturated derivative, eg, cholenate. The metabolism of LASO₄ by microflora from an individual consuming a low beef diet (LBD) was far less extensive than that by microflora from the individual on the HBD; the substrate was metabolized to an intermediate extent by the microflora from an individual consuming a vegetarian diet (VD). The ability of the donor's microflora to form cholانات/ cholenates from LASO₄ decreased in the order: HBD > VD > LBD. (29 refs)

79-6163 Genetic Effects of Formaldehyde in Yeast. III. Nuclear and Cytoplasmic Mutagenic Effects. (Eng) Chanet, R. (Institut Curie-Biologie, Centre Universitaire, Batiment 110, 91405 Orsay, France); von Borstel, R. C. *Mutat Res* 62(2): 239-253; 1979.

The nuclear mutagenic effects of formaldehyde (FA) in yeast strains having different repair capacities were studied. Low concentrations of FA induced nuclear mutations in yeast cells, the induction of reversions being a linear function of the FA concentration and dependent upon the repair capacities of the treated cells. A strain defective in excision repair (*rad3-12*) was more mutable by FA than was the isogenic wild type, whereas a strain with a block in the mutagenic pathway (*rad6-1*) was not mutable after similar treatment. Allele specificities were found; in particular, the *lys1-1* mutation was not reversible by FA. Higher concentrations of FA efficiently induced the cytoplasmic "petite" mutation under nongrowing conditions in which a lethal effect was observed. The growth phase as well as the physiological state influenced this mutagenic effect. (46 refs)

79-6164 Calcium Dependence of Hormone-stimulated cAMP Accumulation in Intact Glial Tumor Cells. (Eng) Brostrom, M. A. (Dept. Pharmacology, Rutgers Medical Sch., Coll. Medicine and Dentistry of New Jersey, Piscataway, NJ 08854); Brostrom, C. O.; Wolff, D. J. *J Biol Chem* 254(16): 7548-7557; 1979.

The role of calcium ion in the regulation of cyclic AMP (cAMP) synthesis in response to norepinephrine (NE) in intact C6 rat glial tumor cells was studied. The Ca²⁺ content of the C6 cells was reduced approx fivefold after repeated treatment with media containing ethylene glycol bis(β -aminoethyl ether) N,N'-tetraacetic acid (EGTA), but there was no loss of cell viability. The ability of the cells to accumulate cAMP in response to β -adrenergic receptor agonists was reduced 60%-70% following Ca²⁺ depletion. The effects of Ca²⁺ appeared to be exerted on components of the adenylate cyclase system other than the catecholamine receptor.

Micromolar free Ca²⁺ concentrations in the extracellular medium were sufficient to restore a maximal NE response to Ca²⁺-depleted cells. Cells in media containing Ca²⁺ exhibited a characteristic biphasic time course of cAMP accumulation; in Ca²⁺-depleted cells, cAMP accumulated more slowly and the subsequent decline in cAMP concentration was also reduced. Verapamil, an inhibitor of plasmalemmal Ca²⁺ influx, decreased the Ca²⁺-dependent component of cAMP accumulation when added prior to the cation. The effect of Ca²⁺ on cAMP accumulation was reduced more extensively by pretreatment at 45 C under Ca²⁺-depleted (80% loss) than under Ca²⁺-restored (30% loss) conditions. Trifluoperazine (15 μ M) decreased the Ca²⁺-dependent increment in cAMP accumulation in Ca²⁺-restored cells. This inhibition was not overcome by increasing NE or extracellular Ca²⁺ concentrations. (44 refs)

79-6165 Tissue Specificity in Metabolic Activation. (Eng) Bartsch, H. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, 69008 Lyon, France); Sabadie, N.; Malaveille, C.; Camus, A. M.; Brun, G. *Adv Pharmacol Ther* 9: 93-102; 1979.

A model for the organospecificity of chemicals is proposed based on data from several systemically acting carcinogens: N-nitrosamines, N-(α -acyloxy)alkyl-N-alkylnitrosamines, and 3,3-dimethyl-1-phenyltriazene. The organ specificity of certain carcinogenic chemicals can be determined by the half-lives of their ultimate carcinogens, which may act to prevent their distribution in the body by covalent reactions in the organs (cells) in which they are generated. In human liver, large interindividual differences in the activity of carcinogen-activating enzymes were noted. Aryl hydrocarbon-hydroxylase (AHH) activity and microsome-mediated mutagenicity were measured using the hepatocarcinogens N-nitrosomorpholine, N-nitroso-N'-methylpiperazine, and vinyl chloride as substrates. When AHH activity in liver specimens from human subjects was plotted against the respective microsome-mediated mutagenicity for *Salmonella typhimurium*, a positive correlation was obtained for the rate of oxidative benzo(a)pyrene metabolism and mutagenicity in the presence of all three substrates. Thus, differences in tissue-specific activation processes of chemical carcinogens appear to be contributing factors in the production of tumors only in certain organs and may also condition the carcinogenic response in different individuals when they are exposed to the same level of environmental carcinogens. (34 refs)

79-6166 Mutagenic Activation of 2-Acetylaminofluorene by Guinea-Pig Liver Homogenates: Essential Involvement of Cytochrome P-450 Mixed-Function Oxidases. (Eng) Takeishi, K. (Dept. Immunology, Virology, Saitama Cancer Center Res. Inst., Ina-machi, Saitama 362, Japan); Okuno-Kaneda, S.; Seno, T. *Mutat Res* 62(3): 425-437; 1979.

2-Acetylaminofluorene (AAF) was highly mutagenic to *Salmonella typhimurium* strain TA98 when activated by a liver post-mitochondrial supernatant fraction (S9 fraction) from guinea-pigs in spite of the resistance of this species to AAF carcinogenesis and the low capacity of guinea-pig liver for N-hydroxylation of AAF. The mutagenicity was comparable to or higher than that resulting from activation by mouse- or rat-liver S9 fraction and was not enhanced by treatment with cytochrome P-450 inducers (a combination of phenobarbital and 5,6-benzoflavone). In an attempt to understand this unexpected result, the possible role of a

cytochrome P-450 mixed-function oxidase system in the mutagenic activation of AAF by guinea-pig liver (similar to the enzymatic activation occurring in mouse liver) was investigated. The mutagenic activation was completely dependent on the addition of a co-factor, NADPH, to the mutation assay system; completely suppressed by antiserum against NADPH-cytochrome c reductase; and sensitive to a cytochrome P-450 inhibitor, 7,8-benzoflavone. These results indicate that the cytochrome P-450 enzyme system is essentially involved even in the mutagenic activation of AAF by guinea-pig-liver S9 fraction, and the mechanism of action responsible for the observed high mutagenic potential of AAF is discussed based on both these and other data. (39 refs)

- 79-6167 In Vitro Metabolism and Activation of Carcinogenic Aromatic Amines by Subcellular Fractions of Human Liver. (Eng) Dybing, E. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); von Bahr, C.; Aune, T.; Glaumann, H.; Levitt, D. S.; Thorgeirsson, S. S. *Cancer Res* 39(10): 4206-4211; 1979.

The in vitro metabolism and metabolic activation of 2-acetylaminofluorene (AAF), 2-aminofluorene (AF), and 2,4-diaminoanisole (DAA) to mutagenic (for *Salmonella typhimurium* strain TA98) and covalently protein-bound intermediates by subcellular fractions from seven normal human livers were studied. AAF was extensively metabolized by all microsomal samples. 7-hydroxy-2-acetylaminofluorene was the major hydroxylated metabolite, but N-hydroxy-2-acetylaminofluorene (N-hydroxy-AAF) was also formed to a substantial degree, ranging from 4% to 10% of the total metabolites in the seven samples. Electrophoresis of the microsomal fractions revealed several polypeptides with mol wt of 40,000-60,000. Two polypeptides with mol wt of approx 54,000 and 55,000, respectively, corresponded to those seen in rat liver microsomes following pretreatment with 3-methylcholanthrene. The in vitro mutagenicity of AAF in the individual samples corresponded with those of AF and DAA, as did the degree of AAF N-hydroxylation. N-hydroxy-AAF was converted to mutagen(s) by both human liver microsomal and cytosol fractions, presumably via deacetylation. A poor association between the extent of covalent binding of AAF to liver microsomal proteins and the degree of mutagenicity in the *Salmonella* system was observed among the samples, possibly indicating that the reactive metabolite(s) arylating the protein differs from that causing the frame-shift mutation in the bacteria. The results indicate that there are qualitative similarities between the subcellular fractions from human liver and those from rat, mouse, and rhesus monkey. (35 refs)

- 79-6168 Quantitative and Qualitative Aspects of the Binding of N-hydroxy-2-Acetylaminofluorene to Hepatic Chromatin Fractions. (Eng) Schwartz, E. L. (Dept. Pharmacology, Michigan State Univ., East Lansing, MI 48824); Goodman, J. I. *Chem Biol Interact* 26(3): 287-303; 1979.

The binding of N-hydroxy-2-acetylaminofluorene (AAF: 0.03% of the diet or injected ip) to hepatic chromatin fractions of male Sprague-Dawley rats was studied. After a single injection (0.4 μ mol/100 g body wt), AAF was found covalently bound to chromatin RNA, protein, and DNA, the amount of carcinogen bound to RNA being 5-fold greater than that bound to DNA and 10-fold greater than that bound to protein. Loss of carcinogen from RNA was rapid, whereas persistent binding to DNA equal to 15% of the initial values was observed. A glycerol gradient

chromatin fractionation procedure and a selective $MgCl_2$ chromatin precipitation procedure were used to identify DNA-bound carcinogen. Three chromatin fractions were described: template expressed euchromatin, repressed heterochromatin, and highly condensed pelleted heterochromatin. With both fractionation procedures, the initial (2 hr) binding of carcinogen was greatest on the euchromatin DNA. Loss of carcinogen was significantly faster from the euchromatin than from the other fractions. By 10 days after a single injection, the largest amount of bound fluorene residues were located on the pelleted heterochromatin DNA, <5% of the initial values being associated with the other fractions. When AAF was incorporated in the diet, loss from the pelleted heterochromatin DNA was enhanced, and loss from the euchromatin DNA was reduced. Thin-layer chromatography confirmed the covalent nature of the carcinogen modification of DNA and demonstrated two separate carcinogen-purine base adducts: N-(guanine-8-yl)-N-aminofluorene and 3-(guanine-N²-yl)-N-acetylaminofluorene. The proportion of the latter adduct was $23 \pm 1.2\%$ greater on the pelleted heterochromatin DNA than on the other two chromatin fractions ($p < 0.05$). (53 refs)

- 79-6169 Mutagenic Effect of a Chemical on Bacterial Strain of *Salmonella typhimurium* (Ames Test): Method and Results for Several Known Carcinogens. (Fre) Hesbert, A. (Institut National de Recherche et de Securite, avenue de Bourgogne, B.P. no. 27, 54500 Vandoeuvre-les-Nancy, France); Cavelier, C.; Bottin, M. C.; Lemonnier, M. *Arch Mal Prof* 40(3/4): 437-457; 1979.

The mutagenicity of known chemical carcinogens was tested using the *Salmonella typhimurium* strains TA 98, TA 100, TA 1538, TA 1535, TA 1537, and TA 1530, with and without metabolic activation by rat hepatic microsomal fraction. Ames test results were considered positive if the number of revertants per dish exceeded double the number of spontaneous revertants. All substances tested (2-aminofluorene, 2-acetylaminofluorene, 9-aminoacridine, 1-aminoanthracene, 2-aminoanthracene, dibenzo(a,i)pyrene, benzo(a)pyrene, 3-methylcholanthrene, chrysene, 7,12-dimethylbenz(a)anthracene, 4-nitroquinoline-1-oxide, N-methyl-N'-nitro-N-nitrosoguanidine, methylmethane sulfonate, sodium azide, aflatoxin B1, and vinyl chloride) were found to be mutagenic, both with and without metabolic activation. (14 refs)

- 79-6170 Pretreatment with Acetylaminofluorene Enhances the Repair of O⁶-Methylguanine in DNA. (Eng) Buckley, J. D. (Paterson Lab., Christie Hosp., Manchester, England); O'Connor, P. J.; Craig, A. W. *Nature* 281(5730): 403-404; 1979.

Possible interrelationships of two hepatocarcinogens were investigated, at the level of DNA repair. Male Wistar rats (7-8 wk old) were fed a standard diet containing 0.06% 2-acetylaminofluorene (AAF) for 3 wk followed by 1 wk on a normal diet. After three such feeding cycles, the rats received one dose of dimethylnitrosamine (DMN: 1.0, 5.5 or 9.0 mg/kg, ip). The rats were killed at various times over a 48-hr period, liver DNA was isolated, and the amounts of O⁶-methylguanine and 7-methylguanine were determined. Measurement of exhaled radiolabeled CO₂ indicated that the rate of metabolism of [¹⁴C-methyl]-labeled DMN was similar in control and AAF-pretreated rats. At 5 hr, the level of 7-methylguanine was similar in liver DNA from control and AAF-pretreated rats, and the amount

formed was linearly related to dose. The amounts of O⁶-methylguanine were also dose-related but were significantly lower for the AAF-pretreated rats. O⁶-Methylguanine repair was enhanced at each dose level; at 9 mg/kg, this enhancement occurred to such an extent that there was no detectable inhibition of the repair process. The repair of O⁶-methylguanine was relatively more active at lower doses of DMN in the control and AAF-pretreated rats. The enhanced repair seen in the AAF-pretreated rats might be due to the induction of a general repair mechanism or may be explained by the activation of a more specific repair system due to the formation of small amounts of an AAF-adduct at the O⁶-position of guanine in DNA. (19 refs)

- 79-6171 Histochemical Studies on Peroxisomes of Mouse Liver During N,N'-2,7-Fluorenylenebisacetamide Carcinogenesis. (Eng) Gotoh, M. (Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan); Furukawa, K.; Mochizuki, Y.; Tsukada, H. *Tumor Res (Sapporo)* 13: 20-29; 1978.

The histogenesis of hepatic tumors in male ICR/JCL mice fed N,N'-2,7-fluorenylenebisacetamide was examined, and the findings were correlated with changes in peroxisome levels, as demonstrated by 3,3'-diaminobenzidine histochemistry. Hyperplastic areas appeared in periportal regions of the liver lobules containing hypertrophic hepatocytes. Small basophilic and large eosinophilic cells were found in these areas. Histologic and histochemical observations suggest that the latter cells are derived from the former through maturation. Small tumors (<2 mm in diameter) also consisted of both types of cells, and they lacked histologic evidence of malignancy. With ethyl- α -p-chlorophenoxyisobutyrate administration, peroxisomal proliferation was induced in these cells, especially in the larger cells. Tumors >2 mm in diameter showed a more complex histologic pattern. Some tumors resembled Walker's type A tumor, and others showed either a mixture of type A areas and areas of small hyperbasophilic cells or a mixture of basophilic and eosinophilic cells with considerable cell atypia and mitotic figures. Histologically, these tumors are considered malignant, except for the type A-like tumors. The number of peroxisomes varied depending on whether basophilic or eosinophilic cells were present, which suggests that peroxisome level is correlated with the degree of cell differentiation. However, the induction of peroxisomal proliferation was almost lost in these tumor cells. (24 refs)

- 79-6172 α -Fetoprotein Levels and Hepatic Alterations During Chemical Carcinogenesis in C57BL/6N Mice. (Eng) Becker, F. F. (Dept. Pathology, Univ. Texas System Cancer Center, Houston, TX 77030); Sell, S. *Cancer Res* 39(9): 3491-3494; 1979.

The hepatic alterations and α -fetoprotein (AFP) levels induced by the insecticide chlordane (CRD, 25 or 50 ppm in the feed) and the chemical hepatocarcinogen acetylaminofluorene (AAF, 0.045% or 0.03% of the diet) were compared using male C57BL/6N mice. Mortality was generally higher among mice given the higher dose of each drug; death was frequently related to pneumonia. Benign proliferative lesions (BPL) were observed in 7% of the mice given 50 ppm CRD, 2% of those given 25 ppm CRD, 4% of those given 0.045% AAF, and 2% of those given 0.03% AAF. Significant elevations in serum AFP were observed in 8% of AAF-treated mice, usually after 52 wk of treatment, and in 15% of CRD-treated mice, usually after 38 wk of treatment. Every mouse with a

malignant lesion had elevated AFP levels, and every mouse with elevated AFP levels demonstrated a malignant lesion. However, none of the mice with BPL alone and none of those receiving transplanted primary hepatocellular carcinomas (PHC) had elevated AFP levels. PHC were detected in 18% of AAF-treated mice, usually after 61 wk of treatment, and in 27% of CRD-treated mice, usually after 48 wk of treatment. The PHC were generally well differentiated with trabeculae. Three of six AAF-induced PHC and 5/12 CRD-induced PHC demonstrated growth after transplantation into new hosts. (22 refs)

- 79-6173 Metabolic Activation of Arylhydroxamic Acids by N-O-Acyltransferase of Rat Mammary Gland. (Eng) King, C. M. (Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI 48201); Traub, N. R.; Lortz, Z. M.; Thissen, M. R. *Cancer Res* 39(9): 3369-3372; 1979.

The lactating mammary glands of rats contain an arylhydroxamic acid N-O-acyltransferase that catalyzes the formation of arylamine-substituted nucleic acid on incubation with N-hydroxy-N-2-acetylaminofluorene or N-hydroxy-N-4-acetylaminobiphenyl and transfer RNA. The acyltransferase activity migrates as a single component with a mol wt of 28,000 on gel filtration on Sephadex G-100. Acyltransferase activities of the lactating mammary glands of Sprague-Dawley rats were approx twice those of the less susceptible Fischer strain, as determined by assay with either hydroxamic acid. The fluorene substrate was 15 times as efficient as the biphenyl compound in promoting adduct formation. Ribosomal RNA adducts formed in vivo after administration of N-hydroxy-N-2-acetylaminofluorene were consistent with an acyltransferase mechanism of activation, in that the adducts did not retain the acetyl group. (20 refs)

- 79-6174 DNA-Damaging and Mutagenic Effect of 1,2-Dimethylhydrazine on *Bacillus subtilis* Repair-deficient Mutants. (Eng) Felkner, I. C. (Dept. Biological Sciences, Texas Tech Univ., Lubbock, TX 79409); Hoffman, K. M.; Wells, B. C. *Mutat Res* 68(1): 31-40; 1979.

1,2-Dimethylhydrazine (DMH) was assayed for mutagenicity and DNA-damaging effects in several *Bacillus subtilis* repair-deficient mutants. The in vivo DNA-repair assay demonstrated that the *B. subtilis* *recA8* and *MC-1* strains were killed at a frequency over 300-fold that of the wild-type parent. Since these *Rec⁻* strains are isogenic with the wild-type strain, except for the reduced ability to repair DNA damage, it is inferred that the increased killing was due to a DNA-damaging effect. DMH was mutagenic to *B. subtilis* strain TKJ6321 at several concentrations with and without metabolic activation. Metabolic activation reduced the mutagenicity significantly. The DNA isolated from a DMH-treated *Rec⁻* strain had altered spectroscopic characteristics and gave a greatly reduced transformation efficiency. Treatment of a wild-type strain with DMH did not alter the spectroscopic properties and had little effect on transformation. These studies show that DMH can alter DNA in vivo, exert DNA-damaging activity, and cause a mutagenic response in repair-deficient strains of *B. subtilis*. These activities are pH-dependent, pH 6.5 giving an optimum response. It seems likely, therefore, that pH is an extremely important determinant in colon tumor initiation by DMH. (29 refs)

- 79-6175 The Oncological Characteristics of Colonic Polyps in Humans in View of Morphogenesis of Experimental

Intestinal Tumors. (Eng) Pozharisski, K. M. (Lab. Experimental Tumors, Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad 188646, USSR); Chepick, O. F. *Tumor Res (Sapporo)* 13: 40-56; 1978.

The morphology and morphogenesis of intestinal epithelial tumors induced by 1,2-dimethylhydrazine in >2,000 rats and of 1,415 polypoid lesions in the human colon and rectum were compared. The development of experimental cancer starts with expansion of the proliferative zone in the intestinal crypts. The first lesion to occur is carcinoma in situ (CIS), which develops in the superficial layers of the flat mucosa. Further evolution of CIS with invasion of the lamina propria leads to superficial cancer development. Invasive cancer develops when neoplastic structures extend into the submucosa. Therefore, experimental intestinal adenocarcinoma appears de novo. Morphogenetic studies showed that the preinvasive stage may persist for a long time. In such cases, structural and cytological signs of epithelial atypism and pleomorphism may be of vital importance for the detection of malignancy. With noninvasive polypoid lesions in humans, emphasis should be placed on detection of the following morphologic manifestations of atypia: a considerable decrease or absence of goblet cells, epithelial pseudostratification or even a multilayered structure, mitoses in the superficial areas of tumors and an increasing proportion of abnormal mitoses, appearance of papillary and villous structures and changes in their configuration, bizarre outlines of tumor glandules, cellular and nuclear polymorphism, and the appearance of cribriform structures, numerous plasma cells, and karyorrhexis-affected lymphocytes in the tumor stroma. Invasion was detected in 70% of the dissected intestinal segments in which these changes were observed upon biopsy. No morphologic signs of malignancy were detected in adenomatous polyps. However, CIS and superficial cancer in a background of intact flat mucosa were quite frequent. Sometimes even very small (2-3 mm in diameter) exophytic neoplasms showed morphologic signs of malignancy, including invasion. These findings suggest that polypoid cancers and glandular villous tumors are malignant from the beginning. In the absence of invasion, they may be identified as CIS or superficial cancer. (91 refs)

79-6176 Effect of Dietary Fiber on the Induction of Colorectal Tumors and Fecal β -Glucuronidase Activity in the Rat. (Eng) Bauer, H. G. (Dept. Surgery, Univ. Hosp. Lund, S-221 85 Lund, Sweden); Asp, N. G.; Oste, R.; Dahlqvist, A.; Fredlund, P. E. *Cancer Res* 39(9): 3752-3756; 1979.

The effects of three types of dietary fiber -- wheat bran (WB, 20% of the basic diet), carrot fiber (CF, 20% of the basic diet), and citrus pectin (CP, 6.5% of the basic diet) -- on the induction of colorectal tumors in male Sprague-Dawley rats by 1,2-dimethylhydrazine (DMH, 15 mg/kg/wk for 12 wk, sc) were studied. The dry fecal weights of the rats fed CF and CP were slightly higher than those fed control diets, and those of rats fed WB were two-fold greater. Tumors were detected in 87%-97% of all rats, the frequency of tumors being significantly higher in the group given CP. In about 25%-30% of the cases, the tumors were located in the proximal colon. They were primarily infiltrating adenocarcinomas of two types, endophytic and exophytic. There were few metastases. Adenocarcinomas in situ were also observed, as were adenomas. In each group of rats, approx 20 infiltrating adenocarcinomas of the small intestine were observed, and tumors in front of the outer orifice of the ear duct were seen in about 15-20 rats in each group. The frequency of ear duct tumors was higher in the CP group. Weight gain and food consumption were the same in all groups, and there were no differences in the β -glucuronidase

(BGC) activities of the ileum or colon between groups. However, feces from the rats fed CP had significantly higher BGC activities than did the feces from other groups. Fecal BGC activity might be one factor of importance in the activation of DMH. (18 refs)

79-6177 A DNA-binding Protein Class Appearing in DMH-induced Carcinogenesis. (Eng) Allfrey, V. G. (Rockefeller Univ., New York, NY 10021); Boffa, L. C.; Vidali, G. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, R. W., ed. (New York; Elsevier): 590 pp.; 351-367; 1978.

Changes in the composition and rates of synthesis of nuclear proteins in the crypt epithelial cells during 1,2-dimethylhydrazine (DMH)-induced colonic carcinogenesis in the rodent were studied. Two protein classes of mol wt 44,000 (TNP1) and 62,000 (TNP2) were selectively synthesized at accelerated rates early in carcinogenesis. TNP1 was found in the dividing tumor cell population, whereas TNP2 was enriched in the nondividing cell population. TNP1 showed a high affinity for DNA and was partially purified by DNA-affinity chromatography. Limited digestions of adenocarcinoma nuclei with DNase I led to a preferential release of TNP1 proteins without a corresponding release of the TNP2 cells. Thus, the TNP1 proteins appear to be associated with the transcribing regions of the genome in the tumor cell nuclei. Levels of histone acetylation were altered in vivo by exposing cultured tumor cells to sodium butyrate, an inhibitor of histone deacetylase activity. DNA in acetylated chromatin was much more susceptible to DNase I attack, and the multi-acetylated forms of the key nucleosomal histones H3 and H4 were preferentially released at early times. Specific sets of nonhistone nuclear proteins, including TNP1 and members of the high-mobility group, were released at the same time. (52 refs)

79-6178 The Demonstration of a Cooperative Action of Bacterial and Intestinal Mucosal Enzymes in the Activation of Mutagens. (Eng) Mc Coy, E. C. (Dept. Microbiology, New York Medical Coll., Valhalla, NY 10595); Petrullo, L. A.; Rosenkranz, H. S. *Biochem Biophys Res Commun* 89(3): 859-862; 1979.

The possibility of a cooperative action of bacterial and intestinal mucosal enzymes in the conversion of 2-aminofluorene and 2-aminoanthracene to mutagens was investigated. Mutagenic activity for *Salmonella typhimurium* TA1538 was determined by the Ames procedure using the usual rat liver microsome preparation, microsomes from rat intestinal mucosa (IM), a cell-free extract derived from a human strain of *Bacteroides fragilis* (Bf), or a combination of Im and Bf. Both test chemicals were readily converted to mutagens by the liver microsomes, but the microsomes prepared from the intestinal mucosa had little or no such activity. The cell-free bacterial extracts exhibited various levels of activity. However, mixtures of the intestinal and bacterial enzyme preparations consistently showed activities that were not only significantly higher than the activity of either preparation alone but also were more than additive, presumably demonstrating a synergistic action. It is suggested that anaerobic bacteria in the colon may convert a colon-specific carcinogen to a penultimate metabolite that could then be transformed to the ultimate form by intestinal enzymes. (8 refs)

- 79-6179 Nitrite-Lipid Reaction in Aqueous System: Inhibitory Effects on N-Nitrosamine Formation. (Eng) Kurechi, T. (Tokyo Coll. Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-30, Japan); Kikugawa, K. *J Food Sci* 44(5): 1263-1266, 1271; 1979.

The chemical interaction of lipids and lipid-containing foods with nitrite in a mild acidic aqueous system was investigated. Methyl linoleate-coated silica gel, Intralipid, cow's milk, mayonnaise, yolk, and miso reduced a considerable amount of nitrite. Methyl linoleate-coated silica gel and cow's milk extensively prevented the formation of carcinogenic N-nitrosamines. The unsaturated fatty acid residues seemed to be responsible for the interaction of lipids with nitrite. Methyl linoleate was changed into two or more unidentified products; neither was the hydroperoxide of the ester. (25 refs)

- 79-6180 Transplacental Mutagenesis of Products Formed in the Stomach of Golden Hamsters Given Sodium Nitrite and Morpholine. (Eng) Inui, N. (Biological Res. Center, 23, Nakogi, Hatano, Kanagawa 257, Japan); Nishi, Y.; Taketomi, M.; Mori, M.; Yamamoto, M.; Yamada, T.; Tanimura, A. *Int J Cancer* 24(3): 365-372; 1979.

Hamster embryos were exposed in utero to the action of sodium nitrite (NaNO_2) and morpholine (Mo) administered simultaneously by stomach tube (500 mg/kg) to the mothers on the 11th or 12th day of pregnancy. Embryo cells were examined for chromosomal aberrations, micronuclear formation, morphological or malignant transformation, and drug resistance mutations. For detection of induced mutations, the embryo cells were cultured in normal medium for 72 hr and then transferred to medium containing 10 or 20 $\mu\text{g}/\text{ml}$ of 8-azaguanine (8AG) or 1 millimolar ouabain (Oua). The number of 8AG-, Oua-resistant colonies was markedly increased after administration of NaNO_2 and Mo. The embryonic fibroblasts also showed a markedly increased frequency of micronucleation and a slight increase in chromosome aberrations. This treatment also caused morphological or malignant transformation of fetal cells. After cultivation in vitro, cells from some transformed colonies produced tumors when inoculated into the cheek pouch of young golden hamsters. N-nitroso-morpholine (N-Mo; 100 or 200 mg/kg, po), used as a positive control, had the same transplacental biological actions on embryonic fibroblasts. However, transplacental administration of Mo alone was ineffective, and the single administration of NaNO_2 had only slight biological effects. N-Mo was produced in the stomachs of animals treated simultaneously with NaNO_2 and Mo. A small amount of the nitrosamine N-nitrosodimethylamine (DMN) was detected in the stomach after a single dose of NaNO_2 . (23 refs)

- 79-6181 Is Acrylonitrile Carcinogenic? (Dut) Aldershoff, W. G. (Volksgezondheid, Hoofdinsektie, Netherlands). *Chem Weekbl* 75(32): 2; 1979.

Acrylonitrile, administered in high doses, was found to be carcinogenic in rats; it induced mainly brain tumors. However, a survey of 700 occupationally exposed workers showed no increase in the cancer risk. According to strict calculations, the annual tumor risk for humans taking doses of up to 0.1 μg acrylonitrile/day lifelong is 1/200,000,000. (no refs)

- 79-6182 N-Nitrosamines in the Rubber and Tire Industry. (Eng) Fajen, J. M. (Div. Surveillance, Hazard Evalua-

tion and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH 45226); Carson, G. A.; Rounbehler, D. P.; Fan, T. Y.; Vita, R.; Goff, U. E.; Wolf, M. H.; Edwards, G. S.; Fine, D. H.; Reinhold, V.; Biemann, K. *Science* 205(4412): 1262-1264; 1979.

Four rubber industry factories (tire chemical, industrial rubber products, aircraft tile, and synthetic rubber and latex) were surveyed for the presence of N-nitrosamines. N-Nitrosodimethylamine (NDMA) was found as an air pollutant at both the chemical factory (0.05-0.5 $\mu\text{g}/\text{m}^3$) and the industrial rubber products factory (0.07-0.14 $\mu\text{g}/\text{m}^3$). N-nitrosomorpholine (NMOR) was found as an air pollutant inside both the chemical factory and the aircraft tire factory at 0-27 $\mu\text{g}/\text{m}^3$. A man doing moderately heavy work near the contaminated area in the tire chemical plant would be exposed to NMOR at 44 $\mu\text{g}/\text{day}$ and to NDMA at 4.8 $\mu\text{g}/\text{day}$. In the most highly contaminated areas of the aircraft tire factory, a similar worker would breathe 260 μg NMOR daily. A typical worker is probably exposed to one-half to one-fifth these levels. Several recent studies have shown increased rates of lung and gastrointestinal (including colorectal) cancers among workers in several work areas where this survey detected the highest amounts of N-nitrosamine contamination. More extensive workplace monitoring must be carried out before one can speculate on the possible involvement of N-nitroso compounds in the etiology of cancer in rubber workers. (17 refs)

- 79-6183 Studies on the Distribution and Metabolism of ^{14}C -Dimethylnitrosamine in Foetal and Young Mice. (Eng) Johansson-Brittebo, E. (Dept. Toxicology, Univ. Uppsala, Uppsala, Sweden); Tjalve, H. *Acta Pharmacol Toxicol (Copenh)* 45(1): 73-80; 1979.

The metabolism of ^{14}C -dimethylnitrosamine (DMN) by the liver of fetal and young C57BL mice was studied in vitro, using $^{14}\text{CO}_2$ production and incorporation of radioactivity into acid-insoluble macromolecules as indices of decomposition. In pregnant mice inoculated with ^{14}C -DMN (2.5 μCi ; 35 μg) whole-body autoradiography was performed with hemisections at -80 C (to prevent evaporation of the volatile DMN) and with dry tape sections (to localize the nonvolatile metabolites). The results indicated that the nonmetabolized substance was transported to the fetal tissues with a uniform distribution and without the formation or accumulation of nonvolatile metabolites. Autoradiography in young (1-10 days old) and adult mice showed a high level of metabolites in the liver 5 min after the administration of ^{14}C -DMN (0.25 $\mu\text{Ci}/\text{g}$; 3.5 mg/kg). No DMN metabolism could be detected in in vitro incubations of liver tissue obtained from fetuses on the last day of gestation. However, in vitro experiments with livers of 1- to 5-day-old mice indicated that there was a rapid increase in enzyme activity after birth. In in vivo studies, there was an increased incorporation of radioactivity in the acid-insoluble macromolecules of the liver and a decreased exhalation of $^{14}\text{CO}_2$ in 10- and 14-day-old mice compared with 21- and 60-day-old mice. Thus, the in vivo metabolism of DMN differs between young and older mice. (19 refs)

- 79-6184 Persistence and Accumulation of (Potential) Single Strand Breaks in Liver DNA of Rats Treated with Diethylnitrosamine or Dimethylnitrosamine: Correlation with Hepatocarcinogenicity. (Eng) Floot, B. G. (Chemical Carcinogenesis Div., Div. Clinical Oncology, Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam,

CHEMICAL CARCINOGENESIS

Netherlands); Philippus, E. J.; Hart, A. A.; Den Engelse, L. *Chem Biol Interact* 25(2/3): 229-242; 1979.

The effects of diethylnitrosamine (DEN) and dimethylnitrosamine (DMN) on the sedimentation pattern of [³H]thymidine-labeled Sprague-Dawley female rat liver DNA in alkaline sucrose gradients were studied with regard to time and dose dependency. In experiments at 1-56 days after a single ip injection, it was observed that potential single strand breaks induced by DEN were repaired at a low rate. At 56 days the sedimentation pattern was still grossly abnormal. Half-life values of 27 and 46 days were observed after 134 mg/kg DEN (approx 45% of the LD₅₀) and 13.4 mg/kg DEN, respectively. Identical experiments after DMN (10 mg/kg, corresponding to about 35% of the LD₅₀) showed almost complete return to control sedimentation patterns within 56 days after injection. Experiments at 6 or 56 days after the last of a series of 5 or 10 weekly injections of DEN (13.4 mg/kg) showed that a major part of DEN-induced damage (measured as single strand breaks) is of a persistent and accumulating character. No accumulation of DMN-induced rat liver lesions was observed. It is concluded that DNA fragmentation and lack of DNA repair is not a consequence of hepatotoxicity. Since at equimolar doses DEN gives appreciably less DNA alkylation (including O⁶-alkylguanine) but is much more effective both as an inducer of preneoplastic liver lesions and as a hepatocarcinogen when compared with DMN, the formation of persistent (and accumulating) DNA damage after DEN administration might be related to the process of liver tumor formation. (15 refs)

- 79-6185 Early Effects of Dimethylnitrosamine on Protein Chain Initiation and Postmicrosomal Polyadenylic Acid-containing RNA Content in Mouse Liver. (Eng) Nygard, O. (Dept. Cell Physiology, Wenner-Gren Inst., Univ. Stockholm, S-113 45 Stockholm, Sweden); Hultin, T. *Cancer Res* 39(9): 3349-3352; 1979.

The early effects of dimethylnitrosamine (DMNA: 17.5, 37.5, and 75 mg/kg) on polypeptide chain initiation and messenger RNA (mRNA) levels in mouse liver were studied in a mouse liver S-30 system. The inhibition of protein synthesis after DMNA administration was associated with a reduced capacity of the S-30 system to form 80S ribosomal initiation complexes. The binding of formylatable methionyl transfer RNA to polysomes was also depressed. In the assay system, the initiation defect was detectable slightly later than the decrease in protein synthesis. Addition of mRNA stimulated both translation and 80S initiation complex formation, but it could not fully restore the activity of the S-30 system from DMNA-treated mice. A loss of polyadenylic acid-containing RNA from the postmicrosomal subfraction of the S-30 fraction was observed as early as 15 min after DMNA administration. Later, polyriboadenylic acid also decreased in the microsomal fraction. Monosomes accumulating in response to DMNA treatment were deficient in mRNA, as determined by polyriboadenylic acid analysis. Conversely, the proportion of polyriboadenylic acid in the remaining polysomes increased, indicating that the mRNA had become less densely occupied with ribosomes. (20 refs)

- 79-6186 Alkylation of DNA and RNA by [¹⁴C]Dimethylnitrosamine in Hydroxyurea-synchronized Regenerating Rat Liver. (Eng) Rabes, H. M. (Inst. Pathology, Univ. Munich, Thalkirchner Strasse 36, 8000 Munich 2, W. Germany); Kerler, R.; Wilhelm, R.; Rode, G.; Riess, H. *Cancer Res* 39(10): 4228-4236; 1979.

Cell cycle-dependent DNA base alkylation and carcinogenic effects in the regenerating male Wistar AF/Hann rat liver were studied following a single ip injection of [¹⁴C]dimethylnitrosamine (DMN, 1.43 mg/kg). Overlapping of cell cycle compartments after partial hepatectomy was prevented by continuous infusion of hydroxyurea (HU), beginning 14 hr after surgery and continuing for up to 25 hr. Metabolic incorporation from DMN via 1-carbon pool differed at various phases in the cell cycle due to changes in DMN metabolism and DNA- and RNA-synthetic activity. A high extent of metabolic incorporation into the adenine and, to a greater extent, guanine of DNA was limited to the period of synchronized DNA synthesis with a rapid decrease in G₂-M. Labeling of purine bases of RNA was maximal during G₁ and G₂-M. The preferential site of alkylation of DNA purine bases was the N-7 of guanine. The molar fraction of 7-methylguanine 2 hr after DMN injection was max in G₁, decreased during S and G₂-M, and was lowest during HU infusion. The molar fraction of O⁶-methylguanine increased during G₁ and showed a rapid decline during S and G₂-M. During DNA synthesis, the ratio of O⁶-methylguanine to 7-methylguanine was significantly lower than during G₀ and G₁, whereas the molar fractions of 7-methylguanine were of the same order of magnitude during G₁, S, and G₂-M. The data suggest that the extent and site of alkylation and also the specific position of a cell in the cell cycle determine the probability of malignant transformation by DMN. Base mispairing as well as an error-prone repair during DNA synthesis could be the mechanism responsible for this process. (66 refs)

- 79-6187 Effect of Urethan, Dimethylnitrosamine, Paraquat, and Butylated Hydroxytoluene on the Aerobic Lactic Acid Production of Mouse Lung and on the Activity of Key Glycolysis Enzymes. (Hun) Arany, I. (Kozegeszsegtani es Jaryanytani Intezet, Debreceni Orvostudományi Egyetem, Debrecen, Hungary); Rady, P.; Bojan, F.; Kertai, P. *Egeszsegtudomány* 23(2): 142-146; 1979.

Urethan and dimethylnitrosamine, which cause lung tumors in CFLP mice, permanently increased aerobic lactic acid production and the activity of key glycolysis enzymes in the mouse lung during the period preceding tumor development. The effect of Paraquat and butylated hydroxytoluene, which do not cause lung tumors, was transitory. Determination of these two parameters appears to be suitable for the rapid in vivo testing of carcinogens. (20 refs)

- 79-6188 Long-Term Experiment of Maximal Non-carcinogenic Dose of Dimethylnitrosamine in Rats. (Eng) Arai, M. (Dept. Pathology, Fujita-Gakuen Univ., Sch. Health Science, Dengakugakubo, Kutsukake-cho, Toyoake, Aichi-ken 470-11, Japan); Aoki, Y.; Nakanishi, K.; Miyata, Y.; Mori, T.; Ito, N. *Gann* 70(4): 549-558; 1979.

The incidence of neoplasms in male and female Wistar rats fed dimethylnitrosamine (DMN, 0.1, 1.0, or 10 ppm in the diet for 96 wk) was studied. The DMN-treated groups did not differ significantly from controls or each other in body wt, food or water consumption, or general condition. The WBC count was increased and the RBC count decreased in rats given 10 ppm DMN, but there were no differences between groups in the results of liver function tests (SGOT, SGPT, alkaline phosphatase, cholinesterase). In rats given >1.0 ppm DMN, nodular hyperplasias of the liver, hepatocellular carcinomas, and hemangioendotheliomas were observed. Pyelonephritis was found in all groups but was most frequent (80%) and severe in males given 10 ppm DMN. The data

suggest that the minimum carcinogenic dose of DMN for the rat is 1.0 ppm in the diet and that the noneffective level is approx 0.1 ppm. (26 refs)

- 79-6189 Systemic Promoting Action and Leukemogenesis in SWR Mice by Phorbol and Structurally Related Polyfunctional Diterpenes. (Eng) Armuth, V. (Experimental Biology Unit, Weizmann Inst. Science, Rehovot, Israel); Berenblum, I.; Adolf, W.; Opferkuch, H. J.; Schmidt, R.; Sorg, B.; Hecker, E. *J Cancer Res Clin Oncol* 95(1): 19-28; 1979.

Six structurally related compounds representing the polyfunctional diterpenes of the tiglane, ingenane, and lathyrane types (phorbol, 4-O-methylphorbol, 12-deoxyphorbol, and 4 α -phorbol; ingenol; and lathyrol and 6,17-epoxylathyrol, respectively) were tested for systemic promoting and leukemogenic activity in SWR mice. For systemic initiation soon after birth, dimethylnitrosamine (DMN, 15 μ g) was injected sc. The diterpenes were administered ip (0.5 μ mole per injection) either with or without prior systemic initiation with DMN. Systemic promotion was expressed for liver by induction of adenomas with all the diterpenes tested, some of which were more potent than phorbol. The relatively high dose of DMN used as initiator prevented an evaluation of promoting action in relation to lung carcinogenesis. The leukemogenic effect of phorbol in SWR mice was confirmed at three different dose levels (0.25, 0.5, and 1.0 μ mole). The other diterpenes tested had no significant leukemogenic activity. The leukemogenic action of phorbol was totally inhibited by prior DMN injection. The lack of correlation between promoting action in skin, systemic promoting action in liver, and leukemogenic action of the diterpenes tested is discussed. (18 refs)

- 79-6190 Sequential Changes in DNA Polymerases α and β During Diethylnitrosamine-induced Carcinogenesis. (Eng) Craddock, V. M. (MRC Toxicology Unit, Woodmansterne Road, Carshalton, Surrey, England); Ansley, C. M. *Biochim Biophys Acta* 564(1): 15-22; 1979.

Sequential changes in DNA polymerases α and β during carcinogenesis induced by diethylnitrosamine (DEN: 90 ppm in the diet for 15 wk) in female Wistar rats were studied. When animals were fed DEN, the "bound" enzymes in the liver fractionated on sucrose gradients in a manner similar to the polymerases isolated from normal liver. Polymerase α activity increased to a maximum 6-9 wk after DEN feeding and then decreased, whereas polymerase β increased throughout the 15 wk of DEN feeding. Within 3 wk after termination of DEN feeding, polymerase β activity had fallen to within the normal range. In rats given DEN, there was an increase in the activity of "soluble" high mol wt polymerase α , the maximum increase at 6-9 wk correlating with the increase in polymerase α in the bound fraction. There was no consistent change in the activity of polymerase β . The results support the views that polymerase α is involved in DNA replication, that the polymerase β functions in repair replication, and that the β enzyme can be induced by chronic DNA damage. (23 refs)

- 79-6191 Mutagenesis by Cytostatic Alkylating Agents in Yeast Strains of Differing Repair Capacities. (Eng) Ruhland, A. (Arbeitsgruppe Mikrobengenetik im Fachbereich Biologie, Johann Wolfgang Goethe-Universität, Robert-Mayer-

Strasse 7-9, 6000 Frankfurt am Main, W. Germany); Brendel, M. *Genetics* 92(1): 83-97; 1979.

Mutation induction by several cytostatic alkylating agents, including nitrogen mustard and its analogs, was studied in depth. Specifically, the reversion of two nuclear ochre nonsense alleles and the cell inactivation induced by these mono-, bi-, and trifunctional alkylating agents and by UV light were investigated in stationary phase haploid cells of yeast strains with differing capacities for DNA repair. The ability to survive alkylation damage correlated with UV repair capacity, a UV-resistant, UV-mutable strain (*RAD REV*) being least sensitive and a UV-sensitive, UV-nonmutable strain (*rad1 rev3*) being most sensitive. The mutagenicity of the alkylating agents was highest in the former and abolished in the latter strain. Deficiency in excision repair (*rad1 rad2*) or in the *RAD18* function did not lead to enhanced mutability. Mutagenesis by the various agents was characterized by a common pattern of induction of locus-specific revertants and suppressor mutants. Induction kinetics were mostly linear, but UV-induced reversion in the *RAD REV* strain followed higher-than-linear (probably "quadratic") kinetics. The alkylating agent cyclophosphamide, usually considered inactive without metabolic conversion, reduced colony-forming ability and induced revertants in a manner similar, but not identical, to that of the other chemicals tested. These findings support the concept of mutagenesis by misrepair after alkylation, which can be distinguished from the mechanism of UV-induced reversion, in spite of their common features. (53 refs)

- 79-6192 Protein Synthesis Inhibition Induced by Dimethylnitrosamine and Diethylnitrosamine on Isolated Rat Hepatocytes. (Eng) Mattei, E. (Biophysical Lab., Inst. Regina Elena Cancer Res., 291, viale Regina Elena, I-00161 Rome, Italy); Delpino, A.; Ferrini, U. *Experientia* 35(9): 1213-1215; 1979.

Isolated hepatocytes from male Sprague-Dawley rats were used to study the inhibition of protein synthesis by dimethylnitrosamine (DMN) and diethylnitrosamine (DENA). Exposure of the cells to high doses of DMN or DENA did not appear to modify the energetic state of the hepatocytes or the leakage of lactic dehydrogenase from the cells. Treatment with either nitrosamine resulted in a definite dose-dependent inhibition of the incorporation of labeled amino acids into acid-soluble material, the inhibition caused by DENA being about 5x greater than that caused by similar concentrations of DMN. After exposure to toxic doses of the two nitrosamines, the inhibited cells progressively recovered their ability to synthesize proteins. The restoration of protein synthetic capability was greater and more rapid after exposure to DENA than after exposure to DMN. (13 refs)

- 79-6193 Effects of Discontinuation of Chronic Feeding of Diethylnitrosamine on the Development of Hepatomas in Adult Rats. (Eng) Barbason, H. (Laboratoire d'Anatomie Pathologique, Université de Liège au Sart-Tilman, 4000 Liège, Belgium); Smoliar, V.; Fridman-Manduzio, A.; Betz, E. H. *Br J Cancer* 40(2): 260-267; 1979.

The effects of discontinuation of chronic feeding of diethylnitrosamine (DENA) on the development of hepatomas in adult male Wistar rats were investigated. The rats were fed 20 mg/kg/day DENA continuously or for periods ranging from 1 to 10 wk. Survival correlated inversely with the duration of car-

CHEMICAL CARCINOGENESIS

cinogen feeding. Less than 4 wk of DENA feeding produced only preneoplastic foci that persisted indefinitely; 4 wk were found to be necessary for the transformation of preneoplastic lesions into liver cancers; after 6 wk, the incidence of hepatomas was 100%. Hepatocarcinogenesis appeared to be identical whether DENA was fed for 8 wk or continuously, up to the time of death. It is suggested that animals treated for <1 mo never developed hepatomas because the normal homeostatic regulation of cell division and function persisting during this first step prevents the growth of foci and their further malignant transformation. Feeding of DENA for >1 mo progressively and irreversibly disturbs this cell control and could, therefore, allow the transformation of foci into neoplastic nodules. DENA treatment beyond the second month has no further effect, perhaps because from this time on, the regulatory mechanism has already been lost and neoplastic development becomes autonomous. (26 refs)

- 79-6194 Induction of Foci of Altered γ -Glutamyltranspeptidase-positive Hepatocytes in Carcinogen-treated Rats Fed a Choline-deficient Diet. (Eng) Sells, M. A. (Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA 15261); Katyal, S. L.; Sell, S.; Shinzuka, H.; Lombardi, B. *Br J Cancer* 40(2): 274-283; 1979.

An attempt was made to determine whether, after exposure of rats to a chemical hepatocarcinogen, feeding a choline-deficient (CD) diet would promote the proliferation of initiated liver cells and the evolution of these cells to foci of altered γ -glutamyltranspeptidase (GGT)-positive hepatocytes. Diethylnitrosamine (DEN), in single doses of 15-150 mg/kg, was injected into intact male Sprague-Dawley rats or rats that had been partially hepatectomized (PH) 18 hr previously. The animals were then fed either a CD or a choline-supplemented (CS) diet for 2-8 wk. Emergence of foci of altered GGT+ hepatocytes was studied by histological and histochemical techniques. Varying numbers of foci developed in the liver of all rats fed the CD diet. The number of foci induced was larger in PH rats than in intact rats. Foci developed in none of the livers of rats fed the CS diet, except in one experiment in which 30 mg/kg DEN was injected into PH rats. In all cases, foci of altered GGT+ hepatocytes were shown to be α -fetoprotein-negative after immunofluorescence staining of liver sections. It is concluded that feeding a CD diet exerts a strong promoting action on the proliferation and further evolution of liver cells initiated by a chemical carcinogen, providing the basis for a new and efficient procedure for the induction of foci of altered hepatocytes in rat liver. (20 refs)

- 79-6195 Carcinogenesis in Tissue Culture 30: Malignant Transformation of Normal Rat Liver Cells Treated with Diethylnitrosamine in Tissue Culture with Special Reference to the Differential Effects of Cytochalasin B on Various Cells with and without Tumorigenicity. (Eng) Katsuta, H. (Japanese Res. Center of Tissue Culture, Dokkyo Univ. Sch. Medicine, Mibu, Tochigi 321-02, Japan); Takaoka, T. *Jpn J Exp Med* 49(3): 187-198; 1979.

Liver tissue from a 14-day-old female F31 rat (inbred strain JAR-2) was cultured for 3 wk and then treated with diethylnitrosamine (DEN: 50 or 100 μ g/ml) for 7 days. After 22 mo of culture, cells were back-transplanted sc into the backs of 4-wk-old F39 and F43 JAR-2 rats (4×10^7 cells/rat). Tumors developed at the inoculation site in every rat; tumors enlarged within 2 mo and caused death in some cases. Metastatic foci, which were histologically diagnosed as

hepatomas, were found in the lung. Chromosome analysis at 5 mo of culture showed that the mode of chromosome numbers in the cells treated with 100 μ g/ml DEN decreased from 42 to 40 and to a triploid range after 21 mo. In cells treated with 50 μ g/ml DEN, the diploid number was maintained at 5 mo but had decreased to 40 by 21 mo. The effects of cytochalasin B were examined using cinemicrography in nine tumorigenic and nontumorigenic cell strains, treated with 1 μ g/ml cytochalasin B during mo 22 through 24. Multinucleated cells were detected in the malignant cell cultures, whereas binucleated cells were abundant in the nontumorigenic cultures. The results indicate that the differential effects of cytochalasin B on tumorigenic and nontumorigenic cells correlates well with the tumor forming capacity of the cells on back-transplantation. (30 refs)

- 79-6196 Carcinogenic Effect of *N*-Nitroso(2-hydroxypropyl)(2-oxopropyl)amine, a Postulated Proximate Pancreatic Carcinogen in Syrian Hamsters. (Eng) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE 68105); Wallcave, L.; Gingell, R.; Nagel, D.; Lawson, T.; Salmasi, S.; Tines, S. *Cancer Res* 39(10): 3828-3833; 1979.

The carcinogenic effect of *N*-nitroso(2-hydroxypropyl)(2-oxopropyl)amine (HPOP) in male and female Syrian golden hamsters was studied. The animals received weekly sc doses of HPOP for life in concentrations of 1/10, 1/20, or 1/40 of the LD₅₀. The LD₅₀ of HPOP was 406.1 mg/kg for females and 353.5 mg/kg for males. All but one HPOP-treated animal developed tumors of types other than those found in controls, and the animals receiving the highest dose died earlier than those treated with the lowest dose. The multiplicity of induced neoplasms seemed to increase at the lower doses because of prolonged survival. Pancreatic tumors appeared in 73%-93% of HPOP-treated hamsters, adenocarcinomas of ductular origin being more common in males than in females. Tumors larger than 5-8 mm were usually invasive and had metastasized to liver or lung. Tumors of the following sites also occurred in HPOP-treated hamsters: nasal cavities (7%-67% of treated animals), larynx-trachea (20%-53%), lungs (67%-93%), lips (0%-40%), forestomach (0%-20%), intestine (0%-20%), liver (0%-60%), gallbladder (13%-33%), kidneys (0%-40%), urinary bladder-urethra (0%-13%), vagina (87%-93%), blood vessels (0%-20%), harderian gland (13%-53%), flank organ (0%-33%), and other (0%-40%). The data suggest that HPOP may be the proximate pancreatic carcinogen following the administration of *N*-nitrosobis(2-hydroxy-propyl)amine or *N*-nitrosobis(2-oxopropyl)amine to hamsters. (26 refs)

- 79-6197 A New *N*-Nitroso Compound, *N*-3-Methylbutyl-*N*-1-methylacetonitrosamine, in Corn-Bread Inoculated with Fungi. (Eng) Lu, S. H. (Cancer Inst., Chinese Acad. Medical Sciences, Peking, China); Li, M. H.; Ji, C.; Wang, M.; Wang, Y.; Huang, L. *Scientia Sinica* 22(5): 601-607; 1979.

A new *N*-nitroso compound, *N*-1-methylacetonitrosamine (*N*-3-methylbutylnitrosamine (MAMBNA), was found in corn bread inoculated with common fungi such as *Fusarium moniliforme*, *Geotrichum candidum*, *Aspergillus terreus*, or *A. flavipes*, which are encountered in the food of Lin Xian County, Henan Province, China. The preliminary identification of this compound by thin-layer chromatography was confirmed by gas chromatography-mass spectrometry. Furthermore, the compound was synthesized and was shown by chemical analysis to be identical to the MAMB-

NA isolated from the corn bread extract. In addition to MAMBA-NA, dimethylnitrosamine, diethylnitrosamine and methylbenzyl nitrosamine were formed in the fungus-inoculated corn bread after an 8-day incubation and the addition of a small amount of sodium nitrite. The presence of precursor compounds for the formation of nitrosamines in moldy maize flour and their significance with respect to the etiology of esophageal cancer in high-risk areas are surveyed. (9 refs)

- 79-6198 Potent Mutagenicity of Urethan (Ethyl Carbamate) Gas in *Drosophila melanogaster*. (Eng) Nomura, T. (Dept. Medical Genetics, Univ. Wisconsin, Madison, WI 53706). *Cancer Res* 39(10): 4224-4227; 1979.

The frequency of gene mutation and translocation induced by urethan (ethyl carbamate) was tested in *Drosophila melanogaster*, and the type of DNA damage produced was investigated. Exposure of spermatozoa to urethan gas induced a high frequency of X-linked recessive lethal mutations detected by the Muller-5 technique, and a clear dose-response was observed. Mutagenic activity of urethan gas on mature spermatozoa following 1.5 hr (2.4% mutations/chromosome) and 5.5 hr (5.5%) of exposure was approx equal to that induced by 1,000 rads (2.3%) and 2,000 rads (5.2%) of γ -radiation. A significant yield of mutations (1.2%) was also seen when germ cells were treated with urethan for 5.5 hr in the spermatogonial stage. Exposure of spermatozoa to urethan gas did not induce a significant yield of translocations, even when the treated sperm was stored in females for more than 10 days; in contrast, γ irradiation, which produced a comparable frequency of X-linked recessive lethal mutations, induced translocations with high frequency. Thus, urethan can barely induce translocation in *Drosophila* germ cells but can strongly induce point mutation. This may be the major cause for the lack of dominant lethals. Mature spermatozoa were exposed to mutagens and eggs were exposed to caffeine at immature stages when eggs are permeable. X-linked recessive lethal mutations induced by 3.5 hr exposure to urethan gas were not reduced by caffeine feeding to females at a low dose (0.5 mg/ml) but significantly reduced at the 5% level by caffeine feeding at a high dose (2.0 mg/ml). When mature spermatozoa were exposed to urethan gas for a longer period (5.5 hr), urethan-induced mutations were slightly reduced by a high dose (2.0 mg/ml) of caffeine, but the difference was not significant. The patterns of caffeine effects on urethan-initiated mutagenesis in *Drosophila* are similar to those of UV- or 4-nitroquinoline 1-oxide-initiated mutagenesis in *Escherichia coli*. (33 refs)

- 79-6199 Mutagenic Activity of Thiram in Ames Tester Strains of *Salmonella Typhimurium*. (Eng) Zdzienicka, M. (Dept. Biochemistry, Warsaw Medical Sch., Banacha 1, 02-097 Warsaw, Poland); Zielenska, M.; Tudek, B.; Szymczyk, T. *Mutat Res* 68(1): 9-13; 1979.

The mutagenic activity of thiram (varying doses, up to 200 μ g/plate) was investigated in 4 histidine-requiring strains of *Salmonella typhimurium* (TA1535, TA100, TA1538, TA98) with and without activation by liver microsomes. In strains TA1535 and TA100, thiram induced mutations without metabolic activation. The presence of rat-liver microsome fraction, cysteine, or glutathione abolished its mutagenic activity in these strains. In contrast, thiram requires metabolic activation for the expression of its mutagenic activity in TA1538 and TA98 strains. The compounds containing the sulfhydryl group abolished mutagenic activity of thiram in these strains also. (10 refs)

- 79-6200 Effect of the Duration of Retinyl Acetate Feeding on Inhibition of 1-Methyl-1-nitrosourea-induced Mammary Carcinogenesis in the Rat. (Eng) Thompson, H. J. (Dept. Home Economics, Pettee Hall, Univ. New Hampshire, Durham, NH 03824); Becci, P. J.; Brown, C. C.; Moon, R. C. *Cancer Res* 39(10): 3977-3980; 1979.

A study was carried out to determine whether continuous treatment is necessary to sustain the inhibition of mammary tumorigenesis produced by retinoid. Female Sprague-Dawley rats received iv injections of 1-methyl-1-nitrosourea (MNU) (50 mg/kg body wt) at 50 and 57 days of age. The animals began receiving a placebo diet or a diet supplemented with retinyl acetate (323 mg/kg diet) 10 days after the first carcinogen injection. Retinoid treatment was either discontinued 60 days after the first injection or continued until day 182 after injection. Retinoid treatment between 10 and 60 days after the first MNU injection prolonged the cancer latency and reduced the av number of cancers per rat, compared with that in controls. Continuation or cessation of retinoid treatment in 60-day tumor-bearing rats had no effect on the time of appearance of additional cancers. In 60-day tumor-free rats, continuation of retinoid treatment prolonged cancer latency in comparison with either 60-day tumor-free rats changed to placebo or rats continuously treated with placebo. The discontinuation of retinoid treatment resulted in a rapid increase in the appearance of cancers; at the termination of the study, the av number of cancers per rat was similar to that in animals fed only the placebo. The data indicate that some rats are more responsive to retinoid treatment than others. Retinoid treatment apparently prevents the progression of early neoplastic lesions, and continuous daily administration appears to be necessary to sustain the protective effect. (10 refs)

- 79-6201 Biochemical Analysis of Experimental Tumor Tissues of the Rat Brain Induced by Ethylnitrosourea. (Jpn) Matsumoto, M. (Second Dept. Surgery, Toho Univ. Sch. Medicine, 6-11-1 Ohmorinishi, Ohta-ku, Tokyo 143, Japan). *Nihon Geka Hokan* 48(4): 459-470; 1979.

A biochemical analysis of the experimentally induced brain tumors in the offspring of female Sprague-Dawley rats injected intraabdominally with ethylnitrosourea (EN) was made in comparison to normal tissue and gliosis tissue from the same rats. Female rats were injected on day 14 of gestation with 50 mg/kg EN, and the offspring were isolated after 120 days and observed. The rate of induction of nervous system tumors was 93%. Tumors were first observed 200 days after birth and developed in the cerebrum in 74.3%, brain stem in 10.5%, and spinal chord in 15.2% of the rats. Mixed gliomas were found in approx 44% of the rats, oligodendroglioma in approx 28%, anaplastic glioma in approx 28%; and 1 rat had an ependymoma-like tumor. The tissue protein content of gliosis tissue and tumor tissue was within the range of controls. The RNA and DNA content in the gliosis tissue was about the same as controls at 1 wk and increased a little by 1 mo, while the RNA/DNA ratio decreased at 1 mo. The RNA and DNA content in the glioma tissue increased, and the RNA/DNA ratio decreased greatly (0.81) compared to gliosis and normal tissue. At 1 wk, the free amino acid level in the gliosis tissue was comparatively normal, and aspartic acid and γ -aminobutyric acid (GABA) levels were low; all three decreased at 1 mo. In the experimental glioma tissue, the aspartic acid, glutamic acid, and GABA levels were low while the glutamine, glycine, and alanine levels were high. In 50% of the glioma tissue specimens, the measurement of GABA was not possible. At 1 wk, the lysosomal enzymes (β -glucuronidase and acid phosphatase) were higher than

CHEMICAL CARCINOGENESIS

normal in gliosis and glioma tissues (β -glucuronidase 15 x normal in glioma) but returned to normal levels by 1 mo. (33 refs)

- 79-6202 The Mutagenicity of Nitrosamides in *Salmonella typhimurium*. (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Andrews, A. W. *Mutat Res* 68(1): 1-8; 1979.

Thirty-four nitrosamides (10 nitrosoalkylcarbamates, 2 nitrosoalkylnitroguanidines, 12 nitrosoalkylureas, 6 substituted nitrosoalkylureas, and 4 cyclic nitrosoalkylureas) were tested for mutagenicity in *Salmonella typhimurium*. All were direct-acting and mutagenic in strain TA1535, with the exception of nitrosophenylurea; its mutagenicity was best demonstrated in strain TA1537. Incubation with a rat-liver microsomal preparation inactivated the nitrosamide and either decreased mutagenicity or left it unaffected. Differences in mutagenic potency among nitrosamides within the same group was in many instances very large and may be partly explained by steric and electronic effects and by the different solubilities of the various compounds. The results show that the mechanism of mutagenesis in bacteria, even by direct-acting alkyl nitrosamides, is complicated. (10 refs)

- 79-6203 Luminal Plasma Membrane Organization in Rat Urinary Bladder Urothelium After Direct Exposure In Vivo to N-Methyl-N-nitrosourea. (Eng) Hainau, B. (Dept. Pathology, Bispebjerg Hosp., Bispebjerg Bakke 23, DK-2400 Copenhagen N.V., Denmark). *Cancer Res* 39(9): 3757-3762; 1979.

The fate of the specialized luminal plasma membrane and junctional complex was analyzed after exposure of rat urothelium to N-methyl-N-nitrosourea (MNU). Adult female Wistar rat urinary bladders were exposed to MNU in vivo (two 1-mg doses instilled in the bladder at an interval of 4 wk). After 12 wk, urothelial hyperplasia was established. Ultrastructural changes in the luminal plasma membrane were studied by thin-sectioning and freeze-fracturing techniques. The mosaic pattern that is a unique characteristic of normal luminal plasma membrane and cytoplasmic vesicles disappeared. The plasma membrane of the transformed urothelium was indistinguishable from undifferentiated membranes in the following respects: thickness; apparent symmetry in cross-section; and distribution of intramembranous particles. Zonulae occludens became permeable to colloidal lanthanum and appeared disassembled, and desmosomes developed concomitantly. These membrane changes indicate that there is increased permeability and less adaptability of urothelial function to mechanical stress caused by bladder volume changes. The increased desmosome formation indicates that squamous metaplasia is a feature of early malignant transformation of the urothelium. It is proposed that MNU alters the plasma membrane assembly and specialization. (29 refs)

- 79-6204 Effect of Dietary Alfalfa, Pectin, and Wheat Bran on Azoxymethane- or Methyl nitrosourea-induced Colon Carcinogenesis in F344 Rats. (Eng) Watanabe, K. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Reddy, B. S.; Weisburger, J. H.; Kritchinsky, D. *J Natl Cancer Inst* 63(1): 141-145; 1979.

The modifying effect of dietary alfalfa, pectin, and wheat bran on azoxymethane (AOM)- and methyl nitrosourea (MNU)-induced colon carcinogenesis was studied in female inbred F344 rats. Weanling rats were fed semipurified diets containing 0% or 15% alfalfa, pectin, or wheat bran. Experimental and control diets also contained 5% alphacel, a cellulose-type nonnutritive fiber, as a source of fiber and 20% corn oil. At 7 wk of age, all animals except controls were given AOM sc at a dose rate of 8 mg/kg/wk for 10 wk or MNU intrarectally at a dose rate of 2 mg/rat twice a week for 3 wk. The AOM-treated group was autopsied 40 wk and the MNU-treated group 30 wk after the first injection of the carcinogen. No tumors were observed in the colon or other organs of untreated rats fed the various diets. Animals fed the alfalfa diet and treated with MNU had a higher incidence of colon tumors than did those fed the control diet or the diets containing pectin or wheat bran. The incidence of MNU-induced colon tumors did not differ between the animals fed the control diet or the diets containing pectin or wheat bran. However, the incidence of AOM-induced colon tumors in rats fed diets containing pectin or wheat bran was lower than that in rats fed the control diet or the alfalfa diet. These results indicate that the effect of fiber in colon carcinogenesis depends on the type of fiber and, possibly, the fiber's mode of action. (27 refs)

- 79-6205 The Relation Between Reaction Kinetics and Mutagenic Action of Mono-functional Alkylating Agents in Higher Eukaryotic Systems. II. Total and Partial Sex-Chromosome Loss in *Drosophila*. (Eng) Vogel, E. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Sylvius Labs., Wassenaarseweg 72, Leiden, Netherlands); Nataraajan, A. T. *Mutat Res* 62(1): 101-123; 1979.

The connection between the primary alkylation patterns and genetic activities of eight monofunctional alkylating agents (AA) was studied using spermatozoa and spermatids of treated *R 1(2), Y B/B⁺ Y y⁺* *Drosophila* males. Ability to produce chromosome aberrations was assessed based on the induction of ring X loss, Y-chromosome loss, and Y rearrangements. The ability to cause chromosomal losses and produce translocations decreased in the sequence methyl methanesulfonate (MMS) = dimethyl sulfate (DMS) > N-methyl-N-nitrosourea (MNU) = N-nitrosodimethylamine (DMA) > ethyl methanesulfonate (EMS) > isopropyl methanesulfonate (iPMS) > N-ethyl-N-nitrosourea (ENU) = N-nitrosodiethylamine (DEN). The low frequencies of Y-chromosome rearrangements made any meaningful comparison between these AA impossible. With MNU, DMN, EMS, MMS, and DMS, a time-dependent increase in the frequencies of ring X losses (storage effect) was observed. Mature spermatozoa tended to be more resistant to the induction of breaks by MNU, DMA, EMS, and MMS. With all AA, a reduced rate of survival of X-bearing sperm was seen after treatment with mutagen. However, there was no apparent quantitative relationship between the shift in the sex ratios and the yield of chromosome aberrations. It is concluded that the differences between these AA in their selectivity for numerous nucleophiles of DNA (indicated by their Swain-Scott *s* values) account for most of the diversity in their genetic effectiveness. Methylation was more effective than ethylation in breaking chromosomes. (20 refs)

- 79-6206 Mutagenicity of Methyl-, Ethyl-, Propyl- and Butylnitrosourea Towards *Escherichia coli* WP2 Strains with Varying DNA Repair Capabilities. (Eng) Garner, R. C. (Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD,

England); Pickering, C.; Martin, C. N. *Chem Biol Interact* 26(2): 197-205; 1979.

The toxicity and mutagenicity of methyl- (MNUA), ethyl- (ENUA), propyl- (PNUA), and butylnitrosourea (BNUA) to *Escherichia coli* WP2 and some of its repair-deficient derivatives were tested in a liquid suspension assay. A comparison of survival rates after nitrosourea exposure between WP2 and WP2 *uvrA* showed no difference between the two strains but a consistent difference in potency between the various nitrosoureas studied. Toxicity increased in the order MNUA < PNUA < ENUA < BNUA. ENUA and PNUA induced a greater number of *trp*⁺ revertants in both strains than did MNUA and BNUA, particularly at low survival rates. None of these differences in biological potency could be accounted for by differences in rates of hydrolysis. ENUA, PNUA, and BNUA were nonmutagenic toward WP2 *lexA*, WP2 *recA*, and WP2 *urA lexA*, whereas MNUA did induce mutations. Ethyl methanesulfonate was able to mutate WP2 *lexA*. (23 refs)

79-6207 Correlation of Biochemical and Morphological Changes Induced by Chemical Injury to the Lung. (Eng) Stewart, B. W. (Sch. Pathology, Univ. New South Wales, P.O. Box 1, Kensington, New South Wales 2033, Australia); Le Mesurier, S. M.; Lykke, A. W. *Chem Biol Interact* 26(3): 321-338; 1979.

Biochemical and morphological changes in female Wistar rat pulmonary alveolar parenchyma induced by N-nitrosomethylurethane (NNMU: 4 mg/kg, iv), 3-methylcholanthrene (MCA: 50 mg/kg, intratracheally), carbon tetrachloride (53,000 mg/m³, 30 min/day for ≤ 15 days, by inhalation), trichloroethylene (TCE: 48,500 mg/m³, 30 min/day for ≤ 15 days), or gasoline vapor (GV: by inhalation) were studied. Single doses of NNMU or MCA inhibited the incorporation of [¹⁴C]orotate into lung RNA 1-3 days after treatment. Daily exposure to CCl₄ to TCE vapor caused a less marked reduction in orotate incorporation, and GV had no significant effect on orotate incorporation. MCA toxicity was characterized by cytoplasmic changes including disruption of surfactant lamellae of Type 2 pneumocytes and variable degenerative changes in Type 1 pneumocytes. At 8-10 days after treatment, the morphological evidence of hypertrophy/hyperplasia and transformation of Type 2 pneumocytes correlated well with biochemical evidence of stimulated [³H]thymidine incorporation. CCl₄ and TCE vapors produced milder changes, including occasional degenerative changes in Type 1 pneumocytes, reduced numbers of surfactant lamella in Type 2 pneumocytes, and no changes in [³H]thymidine incorporation. All chemicals caused a marked and reproducible reduction in secretion of pulmonary surfactant, as determined by endobronchial lavage. Reduced recovery of surfactant was detected after 5 days of solvent inhalation, but no further changes resulted from another 10 days exposure. (32 refs)

79-6208 Effects of Dietary Administration of Chenodeoxycholic Acid on N-methyl-N-nitrosourea-induced Colon Cancer in Rats. (Eng) Sarwal, A. N. (New York Univ. Medical Center, New York, NY); Cohen, B. I.; Raicht, R. F.; Takahashi, M.; Fazzini, E. *Biochim Biophys Acta* 574(3): 423-432; 1979.

The effects of dietary chenodeoxycholic acid (CA: 0.2% by wt of normal diet) upon N-methyl-N-nitrosourea (MNU)-induced colonic tumors and on fecal sterol patterns were studied in male CD

Fisher rats. At 6 wk of age, MNU administration was begun (2 mg/rat intrarectally on days 1, 4, 8 and 11). Twenty-two of 45 rats fed a normal diet had developed colonic tumors at the time of sacrifice (28 wk after the first MNU dose), whereas 26/42 rats fed a CA-supplemented diet and given MNU developed tumors (p < 0.2). Most lesions were adenomatous polyps with some adenocarcinoma in situ; nine polyploid lesions demonstrated invasive carcinomas. Analysis of stools by gas-liquid chromatography-mass spectroscopy showed fecal neutral sterol levels to be elevated in the MNU-treated groups (p < 0.05), irrespective of diet. Feeding the CA diet increased fecal bile acid concentration from 4 mg/g stool in untreated controls to 10.3 mg/g in animals receiving CA (p < 0.025); MNU administration did not have this effect, nor was there evidence that it interacted with the CA diet. Isolithocholic acid was 21% of the total 3-monohydroxy bile acids in rats given CA. In animals fed control diets, isobile acid levels were negligible. The small increase (1 mg/g stool) in secondary bile acid (deoxycholic acid and lithocholic acid) levels may be the reason that CA diets do not greatly increase the incidence of MNU-induced colonic cancer, as do diets containing cholic acid. The profile of fecal bile acids of rats fed a CA diet suggests that the ability of rats to 6- and 7-hydroxylate bile acids may block the promoting effect of dietary CA upon MNU-induced colonic cancer. (21 refs)

79-6209 The Relation Between Reaction Kinetics and Mutagenic Action of Mono-functional Alkylating Agents in Higher Eukaryotic Systems. I. Recessive Lethal Mutations and Translocations in *Drosophila*. (Eng) Vogel, E. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Sylvius Labs., Wassenaarseweg 72, Leiden, Netherlands); Natarajan, A. T. *Mutat Res* 62(1): 51-100; 1979.

The relationship in *Drosophila* males between the chemical reaction patterns of monofunctional alkylating agents (AA) and their biological effectiveness was studied. The ability to break chromosomes decreased in the sequence methyl methanesulfonate (MMS) > dimethyl sulfate (DMS), N-methyl-N-nitrosourea (MNU) > N-nitrosodimethylamine (DMN) > ethyl methanesulfonate (EMS) > isopropyl methanesulfonate (iPMS) > N-ethyl-N-nitrosourea (ENU) = N-nitrosodiethylamine (DEN). When mutagenic effectiveness was determined on the basis of the ratio of the exposure condition producing 4% recessive lethals to the LD₅₀, the sequence was ENU > EMS > iPMS, MNU > MMS = DMS. EMS was slightly less effective in the translocation test and less cytotoxic but more mutagenic in the recessive-lethal test than would be expected based on its Swain-Scott *s* value. This was taken as an indication of the influence on biological effectiveness of factors other than the *s* value, eg, methylation vs ethylation and the lipid:water partition ratio. For those AA that were clearly active in the translocation test, a delayed formation of exchanges was observed. Thus, storage experiments in *Drosophila* are necessary to detect this type of rearrangement by AA. The apparent link between the ability of AA to induce chromosome breakage and to produce delayed mutations indicated the significance of nucleophiles with high *n* values for the initiation of either event. The data indicate that two variables have major significance in determining the quality and frequency of genetic damage of AA in *Drosophila*: dose and reaction pattern (site of alkylation). The molecular events that characterize the action of ENU and DEN on DNA, ie, O-alkylation (in particular, phosphotriester formation), are not critical for the processes leading to chromosome breakage. (87 refs)

79-6210 N-Ethyl-N-Nitrosourea-induced Spinal Tumors in an Inbred Strain of W Albino Rats. (Eng) Pfaffenroth,

M. J. (Dept. Biological Sciences, Lilly Hall Life Sciences, Purdue Univ., West Lafayette, IN 47907); Das, G. D. *J Natl Cancer Inst* 63(3): 647-650; 1979.

The incidence of spinal tumors developing in an inbred strain of W albino rats exposed prenatally to N-ethyl-N-nitrosourea (ENU: 60 mg/kg) on one of days 14-21 of gestation or were given a single postnatal dose (0.2 mg/animal) directly into the cerebellum 6 or 11 days after birth was investigated. Twenty-nine of 34 rats that had been exposed to ENU prenatally and 6/15 rats exposed postnatally developed one or more CNS tumors. Spinal tumors were detected in 14 animals exposed prenatally and 4 exposed postnatally to ENU. In another study, 23/25 animals exposed prenatally to a single dose of 60 mg ENU/kg on day 20 of gestation developed spinal cord tumors. These tumors included relatively pure oligodendrogliomas, astrocytomas, and mixed gliomas. The results suggest that this rat strain has a high susceptibility to the induction of tumors in the spinal cord by ENU and would be a good neural tumor research model. (13 refs)

79-6211 Development of Second Malignancies in Rats After Cure of Acute Leukemia L 5222 by Single Doses of 2-Chloroethylnitrosoureas. (Eng) Zeller, W. J. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Schmahl, D. *J Cancer Res Clin Oncol* 95(1): 83-86; 1979.

The development of secondary malignant tumors in 9/79 BD IX rats cured of rat leukemia L5222 by single doses of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) or 1-(2-hydroxyethyl)-3-(2-chloroethyl)-3-nitrosourea (HECNU) is reported. The drugs (6.3-12.5 mg/kg, ip) were administered late in the course of leukemia development. Malignant secondary tumors developed in 4/36 rats given BCNU and 5/43 rats given HECNU. The tumors included an intraabdominal fibrosarcoma, a meningeal sarcoma, an oligodendroglioma of the brain, an endocardial sarcoma, an intrathoracic adenocarcinoma (metastatic), an adrenal cortical carcinoma, an ovarian carcinoma, a malignant neurinoma of the cauda equina, and a cholangiocellular carcinoma. These secondary malignancies were attributed to nitrosourea therapy and the results suggest that a detailed investigation of the carcinogenicities of clinically used 2-chloroethylnitrosamines is necessary. (9 refs)

79-6212 The Mutagenicity of Nitrosopyrrolidine is Related to Its Metabolism. (Eng) Hecker, L. I. (Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Elespuru, R. K.; Farrelly, J. G. *Mutat Res* 62(2): 213-220; 1979.

Various cell fractions from rat liver were tested for their ability to convert nitrosopyrrolidine (NO-PYR, 5-25 millimolar) to products which were mutagenic to *Escherichia coli* in liquid-incubation assays. Microsomes alone produced only a small number of *tyr*+ revertants (approx 40/10⁸ survivors), while the S₁₀₀ supernatant produced none at all. However, the S₈ fraction or combinations of microsomes and the S₁₀₀ supernatant yielded 300-400 *tyr*+ revertants/10⁸ survivors. Neither products of the microsomal nor of the microsome + supernatant reactions were mutagenic in the absence or presence of cellular fractions. These results suggest that bacterial mutagens are formed during the microsomal metabolism of NO-PYR to 2-hydroxytetrahydrofuran by α -hydroxylation, but not during the metabolism of 2-hydroxytetrahydrofuran by the S₁₀₀ supernatant enzymes. Possible roles of the supernatant en-

zymes in the formation of mutagenic intermediates during the initial α -hydroxylation of NO-PYR are discussed. (29 refs)

79-6213 Dominant Lethal Assay of Some Hair-Dye Components in Random-Bred Male Rats. (Eng) Sheu, C. J. (Genetics Toxicology Branch, Div. Toxicology, Food and Drug Admin., Washington, DC 20204); Green, S. *Mutat Res* 68(1): 85-98; 1979.

Male rats were exposed to maximally tolerated doses of five hair-dye components in a dominant lethal test. Each component was tested at 3 dosage levels with 15 random-bred male rats per level. The highest dose, selected on the basis of subacute toxicity testing, generally reduced weight gains without being lethal. Freshly prepared solutions were injected ip at 1 ml/kg 3x/wk for 10 wk. Rats injected with dimethylsulfoxide and triethylenemelamine served as solvent and positive controls, respectively. A majority of rats survived the treatment at the levels tested and were mated to two virgin females each per wk for 2 wk. The females were sacrificed at midterm of pregnancy and examined for live and dead implants. Dominant lethality was evaluated on the basis of 4 criteria: dead implants per pregnant female, dead implants per total implants, proportion of females with one or more dead implants, and proportion of females with two or more dead implants. 2-Nitro-*p*-phenylenediamine, 2,4-diaminoanisole sulfate, and 2,5-diaminoanisole sulfate produced negative responses, whereas *m*-phenylenediamine and 4-nitro-*o*-phenylenediamine induced weak dominant lethality in the first trial. On retesting these weakly positive components, both *m*-phenylenediamine and 4-nitro-*o*-phenylenediamine produced negative responses. (11 refs)

79-6214 Carcinogenesis in Rat Esophagus by Intraperitoneal Injection of Different Doses of Methyl-n-amylnitrosamine. (Eng) Bulay, O. (Ankara Univ., Tip Fakultesi Patoloji Kursusu, Morfologi, Sihhiye, Ankara, Turkey); Mirvish, S. S. *Cancer Res* 39(9): 3644-3646; 1979.

The carcinogenicity of methyl-n-amylnitrosamine (MNAN) in MRC-Wistar rats was determined after ip injection on a variety of dose schedules. After 6 weekly MNAN injections of 25 mg/kg or 12 weekly injections of 12.5 or 25 mg/kg, the incidence of esophageal squamous cell papillomas was 85%-100% and that of esophageal squamous cell carcinomas was 40%-65%. With 12 injections, the mean survival time was 25-31 wk. Treatment with one or two doses of 50 mg/kg produced a lower incidence (<20%) of esophageal tumors and a longer survival time of 67-77 wk. One 85-mg/kg injection caused esophageal carcinomas in 5/7 rats. The treated groups also had squamous cell papillomas and carcinomas in the nasal cavity (up to 50% incidence) and trachea (up to 30% incidence). Hence, a 6- or 12-wk treatment schedule was adequate for inducing esophageal tumors and could be used for studies of agents modifying esophageal tumor induction by MNAN. (10 refs)

79-6215 Neoplastic and Preneoplastic Lesions in Rats after Oral Administration of a Single Dose of N-Nitrosomorpholine. (Ger) Bannasch, P. (Abteilung fur Cytopathologie, Institut fur Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900

Heidelberg, W. Germany); Mayer, D.; Krech, R. *J Cancer Res Clin Oncol* 94(3): 233-248; 1979.

Tumor development was studied in 62 male Sprague-Dawley rats given a single po dose of N-nitrosomorpholine (NNM: 320 mg/kg). This treatment resulted in the development of neoplastic and preneoplastic changes in different organs, especially the liver and kidney. After a lag period of 4 wk, nearly all experimental animals developed preneoplastic (clear cell, acidophilic, basophilic, mixed cell) foci in the liver parenchyma. Small neoplastic nodules were found sporadically in the liver as early as 4 wk after the beginning of the experiment. After a lag period of 1-2 yr, 4/13 rats showed multiple neoplastic hepatic nodules, and 1 animal had a hepatocellular carcinoma. Mucous cholangiofibroses and cystic cholangiomas occurred in some experimental animals. After long lag periods, large cholangiofibromas were found in two experimental animals. One or two years after carcinogen administration, many animals developed epithelial (clear cell, acidophilic, chromophobic, basophilic, oncocyctic) kidney tumors, which were often cystic. Pathologically changed (clear cell, chromophobic, basophilic, oncocyctic) tubules are regarded to be precursors of epithelial tumors. The altered tubules appeared for the first time about 6 mo after carcinogen administration. In addition to multiple hepatic and renal cysts, two animals developed pancreatic cysts. In addition, two mesenchymal kidney tumors, one malignant neurinoma, two subcutaneous fibromas, one fibroadenoma, and one squamous cell carcinoma of the skin were observed. (43 refs)

- 79-6216 Experimental Induction of Hepatomas, Mammary Tumors, and Other Tumors with Metronidazole in Noninbred Sas:MRC(W1)BR Rats. (Eng) Rustia, M. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42d St. and Dewey Ave., Omaha, NE 68105); Shubik, P. *J Natl Cancer Inst* 63(3): 863-868; 1979.

Metronidazole was tested for carcinogenicity in noninbred Sas:MRC(W1)BR rats. Three groups received the drug for life at dose levels of 0.6%, 0.3%, and 0.06% in a powdered diet. The incidences of mammary tumors and hepatomas increased significantly ($p < 0.020$ and $p < 0.050$, respectively) among females given the highest dose, compared with controls. The rates of Leydig cell tumors of the testes and pituitary adenomas were increased ($p < 0.040$ for both) among males given the highest dose. These results, together with those obtained in other studies, suggest that metronidazole possesses a considerable carcinogenic potential. (34 refs)

- 79-6217 Lack of Evidence for Cancer Due to Use of Metronidazole. (Eng) Beard, C. M. (Dept. Medical Statistics and Epidemiology, Mayo Clinic, 200 First St. SW, Rochester, MN 55901); Noller, K. L.; O'Fallon, W. M.; Kurland, L. T.; Dockerty, M. B. *N Engl J Med* 301(10): 519-522; 1979.

The development of cancer was evaluated in 771 women who were treated for vaginal trichomoniasis with metronidazole (750 mg/day for 10 days) during 1960-1969. Forty cases of cancer were diagnosed in the metronidazole-exposed group during 8,267 person-yr of follow-up evaluation since exposure. Sixteen of these tumors were carcinoma in situ of the uterine cervix. At all other sites as a whole, the number of observed cancers (24) were not significantly higher than expected (21.7 based on the Connecticut Tumor Registry and 18.4 on the Third National Cancer Survey).

Analysis of the observed and expected number of cancers according to specific site showed that the observed number in all sites except the lungs was similar to the expected number. There were four cases of lung cancer compared to the expected 0.6, but the four patients were all smokers. The 11 deaths from cancer in this group were more than expected but not statistically significant. The number of carcinomas of the uterine cervix in patients with a history of trichomoniasis was greater than expected in women without such a history regardless of whether or not they were treated with metronidazole. These data suggest that an increase in cervical cancer may be caused by the underlying infection or some predisposing factor common to both diseases rather than by metronidazole treatment. (39 refs)

- 79-6218 Morphologic Changes of the Gastric Mucosa of Rats After Administration of N-Methyl-N'-Nitro-N-Nitrosoguanidine. Electron Microscopic Study. (Eng) Jakubovsky, J. (Res. Lab. Histochemistry, Komensky Univ., 884 24 Bratislava, Czechoslovakia); Brozman, M.; Zaviacic, M.; Duris, I.; Popperova, E. *Neoplasma* 26(1): 39-47; 1979.

The effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 83 mg/liter in drinking water for 8 wk) on the gastric mucosa were studied in 12 male Wistar rats. The nuclei of the undifferentiated, and to a lesser degree the differentiated epithelial cells were mostly round or oval and occasionally displayed a surface consisting of deep invaginations or intranuclear cytoplasmic pseudoinclusions containing different organelles. In such nuclei, disappearance of parts of the outer nuclear membranes was generally observed. Thin bands of peripheral condensed chromatin extended far into the peripheral cytoplasm; these bands were not surrounded by nuclear membranes. An increased amount of perichromatin and interchromatin granules was observed in the chromatin. The nuclear membranes contained predominantly irregular broad perinuclear cisterns; these were occasionally bridged by porous complexes, the number of which varied from one area to another. In the cytoplasm of differentiated epithelial cells, autophagous processes were observed, and in the undifferentiated neck cells, large amounts of polysomes and profiles of diversely deformed rough endoplasmic reticulum were seen. These cells showed marked proliferative activity. The changes described in the nuclei of the epithelial cells were also observed in the nuclei of some smooth muscle cells, fibrocytes, and eosinophils, where the nuclear material was localized below the cell surface and the cytoplasm was found within limited spaces. (24 refs)

- 79-6219 High Concentrations of Glutathione in Glandular Stomach: Possible Implications for Carcinogenesis. (Eng) Boyd, S. C. (Field Studies and Statistics Program, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20205); Sasame, H. A.; Boyd, M. R. *Science* 205(4410): 1010-1012; 1979.

The concentrations of reduced glutathione (GSH) in the glandular stomach of male Sprague-Dawley rats, measured in the late afternoon, was 7.23-8.26 mM, which is similar to that seen in the liver and exceeded that of all other tissues. Gastric GSH varied diurnally; concentrations were highest in the late afternoon and lowest at night and early morning. Starvation (48 hr), depletion of hepatic GSH by diethyl maleate (DEM) treatment, or stress by physical restraint for 4 hr in the cold caused marked decreases in GSH. Prior treatment of animals with cobaltous chloride caused a marked increase in gastric and hepatic GSH concentrations. The

CHEMICAL CARCINOGENESIS

resistance of the glandular gastric mucosa of laboratory rodents to carcinogens, such as the polyaromatic hydrocarbons (PAH), might be due to the relatively low GSH concentration in the squamous portions of the stomach, which are highly susceptible to PAH compounds, since GSH deactivates carcinogenic PAH metabolites. It is also possible that the high susceptibility of the glandular stomach to carcinogens such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) might be directly related to the high GSH content of that portion of the stomach, since a previous study showed that GSH strongly stimulates DNA alkylation by MNNG in vitro. (19 refs)

- 79-6220 Oncogenic Transformation in Epithelial Cell Lines Derived from Tracheal Explants Exposed In Vitro to N-Methyl-N'-nitro-N-nitrosoguanidine. (Eng) Steele, V. E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Marchok, A. C.; Nettesheim, P. *Cancer Res* 39(10): 3805-3811; 1979.

To investigate oncogenic transformation of respiratory tract epithelium in vitro, tracheal explants from specific-pathogen-free Fischer 344 rats were exposed to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0, 0.001, 1.0, or 10.0 µg/ml medium) for 6 hr on days 3 and 6 of culture. Primary epithelial cell cultures, derived from 25/30 carcinogen-exposed explants, underwent a distinct morphological change after approx 160 days of culture. Only after this change could primary cell cultures be subcultured into cell lines. No cell lines could be established from control tissues. The tumorigenicity of the cell lines was determined after approx 10 or 20 passages by inoculation of 10⁶ cells into immunosuppressed syngeneic rats. The number of explants that yielded tumorigenic cell lines was 0, 5, 6, and 9, respectively, for groups of 10 animals exposed to 0, 0.001, 1.0, and 10.0 µg/ml MNNG. The av latency period between inoculation and tumor appearance was also dose-related; it was significantly shorter for cell lines in the group receiving 10 µg MNNG/ml (56 ± 21 days) than for cell lines in the group receiving 0.001 µg/ml (108 ± 13 days, p < 0.05). Either adenosquamous cell carcinomas or keratinizing squamous cell carcinomas were obtained from cell lines in all groups. Four cell lines in the group receiving 10 µg MNNG/ml and two cell lines in the group receiving 1 µg/ml formed tumors that metastasized to other organs. During culture, cell lines became increasingly malignant, as demonstrated by inoculation of some of the cell lines at successive passages; in all cases, tumor incidence increased and the latency period decreased with increasing passage number. The high frequency of transformation, the dose response, and the production of differentiated epithelial tumors achieved make this culture system a valuable tool for studying the oncogenic transformation of respiratory tract epithelium in vitro. (22 refs)

- 79-6221 Early Proliferative Changes in Rat Pyloric Mucosa Induced with N-Methyl-N'-Nitro-N-Nitrosoguanidine (MNNG). (Eng) Deschner, E. E. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Tamura, K.; Bralow, S. P. *Front Gastrointest Res* 4: 25-31; 1979.

The early proliferative changes occurring prior to and during gastric tumor formation were studied in random bred Wistar rats given N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 83 mg/liter) in the drinking water for 15 wk. After 10 wk of MNNG administration, the rats showed a downward shift in the distribution of the proliferative compartment in the pyloric mucosa. Histologically atypical pits lined with cuboidal mucous-depleted epithelial cells which demonstrated increased proliferative activity

were also observed at 10 wk. At 10 and 15 wk, the labeling indices of these pits were elevated two- to fivefold over control levels. Early invasive adenocarcinomas were noted at both 10 and 15 wk. Tumor cells actively penetrating the muscularis mucosa appeared to be more actively engaged in DNA synthesis than tumor cells confined within the mucosa. If the mechanism and development of gastric cancer in man are similar to those observed in this animal model, there is little hope for improving the 5-yr survival statistics. (8 refs)

- 79-6222 Sequential Histopathology and Cell Kinetic Changes in Rat Pyloric Mucosa During Gastric Carcinogenesis Induced by N-Methyl-N'-nitro-N-nitrosoguanidine. (Eng) Deschner, E. E. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Tamura, K.; Bralow, S. P. *J Natl Cancer Inst* 63(1): 171-179; 1979.

The effect of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 83 mg/liter drinking water) on the pyloric mucosa of male noninbred Wistar rats was followed. Autoradiographic studies were made of animals killed after 10, 15, 26, and 36 wk of treatment. In the normal-appearing mucosa of rats treated with MNNG for 10 wk, the number of epithelial cells per pit column was significantly increased over that in controls. Simultaneously, a shift in the major zone of epithelial cell proliferation was noted in the treated rats. Along with the formation of a longer pit in MNNG-treated rats, the greatest number of DNA-synthesizing cells was displaced from the middle third of the pit in a downward direction toward the muscularis mucosa. In addition, at this early experimental time period, pits lined with more immature, cuboidal, mucus-depleted cells were recognizable. These pits not only had higher labeling indices than normal-appearing pits of the same animals, but they also had a dual nature, with increased proliferative activity extending either upward to the luminal surface or further in a downward direction. Focal areas of cellular atypism, present by week 10 of treatment, had a three- to sevenfold greater DNA synthesis activity than that found in the normal-appearing mucosa of the same animal. A wide range of proliferative activity was found not only among invasive pyloric tumors within the same animal, but also within different areas of the same tumor. The mechanism for the formation of adenomas and invasive adenocarcinomas is believed to be related to the dual character of the hyperplastic pits. (25 refs)

- 79-6223 Effect of Aging on the Development of N-Methyl-N'-nitro-N-nitrosoguanidine-induced Gastric Cancer in Rats. (Eng) Kimura, M. (Dept. Surgery, 617-1, Takahayashi, Gunma Cancer Center, Ota, Gunma-ken 373, Japan); Fukuda, T.; Sato, K. *Gann* 70(4): 521-525; 1979

The effect of aging on the induction of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) gastric carcinogenesis was studied in male Wistar rats. Three groups of rats, aged 6, 20, and 40 wk, were used. All groups received MNNG in the drinking water (83 mg/liter) for 30 wk. The gastrointestinal tumor incidences were 94.7%, 73.8% and 48.8% at 6, 20, and 40 wk of age, respectively; tumor incidence in the two older groups was significantly decreased (p < 0.01) compared with that in the youngest group. The incidence of glandular stomach adenocarcinomas was also significantly decreased (p < 0.01) in the younger groups (86.8%, 50%, and 39.4% in 6-, 20-, and 40-wk-old animals, respectively). The rate of MNNG intake per gram body wt was higher in the youngest group during the first 25 wk than in the 20-wk-old rats.

However, even when the dose was adjusted to that of the older rats, the tumor incidence was unaffected. It is concluded that aging may reduce the incidence of MNNG-induced gastric cancer in rats. (10 refs)

- 79-6224 Effects of Arginine Deprivation Upon Chromosome Aberrations, SCEs and Survival of CHO Cells Treated with Mutagenic Agents. (Eng) MacRae, W. D. (Environmental Carcinogenesis Unit., B.C. Cancer Res. Centre, Vancouver, B. C., Canada); MacKinnon, E. A.; Stich, H. F. *Mutat Res* 62(3): 495-504; 1979.

Arginine deprivation sensitized CHO cells to the clastogenic activity of the mutagenic agents UV light, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), mitomycin C and 4-nitroquinoline-1-oxide. Cells were allowed to undergo proliferative arrest by arginine deprivation, then were treated with mutagenic agent and refed with complete medium. The resulting mitotic cells displayed more chromosome aberrations than did mitotic cells in proliferating cell cultures treated similarly with mutagens. This effect was observed at each dose tested (representing a 300-fold range in concentration). Survival of arginine-deprived cells exposed to UV light was also markedly reduced in comparison to the response of proliferating cells. Sister-chromatid exchange levels induced by MNNG, in contrast, were similar in arginine-deprived and proliferating cells. (22 refs)

- 79-6225 Species Variation in BrdUrd-induced Sister-Chromatid Exchanges. (Eng) McFee, A. F. (Comparative Animal Res. Lab., Oak Ridge, TN 37830); Sherrill, M. N. *Mutat Res* 62(1): 131-138; 1979.

Species variation in 5-bromodeoxyuridine (BrdUrd)-induced sister-chromatid exchanges was studied. Peripheral blood lymphocytes from cattle, pigs, sheep, and humans were cultured in the presence of 0.5, 1, 2, 5, 10, or 20 $\mu\text{g/ml}$ of BrdUrd. Sister-chromatid exchanges were scored in 25 second-division metaphases from each donor at each level of the chemical. Dose-response curves for all four species increased steeply to 2 $\mu\text{g/ml}$; above this level, SCE numbers increased less rapidly but maintained a linear relationship to increasing BrdUrd concentrations. Comparisons of the straight-line portions of the dose-response curves showed that human cells were significantly more sensitive to increasing BrdUrd concentrations than cow or pig cells and different from sheep cells at the 10% confidence level. (19 refs)

- 79-6226 Effects of Caffeine on Chromosome Aberrations and Sister-Chromatid Exchanges Induced by Mitomycin C in BrdU-labeled Human Chromosomes. (Eng) Shiraishi, Y. (Lab. Cell Biology, Dept. Anatomy, Kochi Medical Sch., Nagoku-City, Kochi 781-51, Japan); Yamamoto, K.; Sandberg, A. A. *Mutat Res* 62(1): 139-149; 1979.

The 5-bromodeoxyuridine (BrdU) - Hoechst staining technique was used to analyze the effect of caffeine (CAF) on chromosome aberrations and sister-chromatid exchanges (SCE's) induced by mitomycin C (MC) in lymphocytes from normal individuals. CAF increased the frequency of SCE's in MC-treated chromosomes in all specimens. The combination of MC and CAF markedly increased all types of chromosome aberrations, but the most startling effect was the appearance of many cells with multiple aberra-

tions (shattered chromosomes). The BrdU-Hoechst technique showed that the shattered chromosomes did not appear in cells that had replicated only once, but they did occur in cells that replicated twice in the presence of MC and CAF. The large majority of chromatid breaks did not involve areas common to SCE's, and the SCE frequency significantly increased in spite of the existence of multiple breaks. This indicates that very few of the breaks are incomplete exchanges and that the mechanism for the formation of SCE's might be different from that of chromosome breaks. In another experiment, monofunctional MC had a small effect on SCE rates, although it induced shattered chromosomes in combination with CAF. Possible differences in the mechanisms leading to SCE's and chromosome breaks are discussed. (27 refs)

- 79-6227 Inhibition by Oncornavirus of a System of DNA Repair Induced by the Chemical Carcinogen 4-Nitroquinoline-1-oxide. (Rus) Andzhaparidze, O. G. (Res. Inst. Virus Preparations, Moscow, USSR); Zasukhina, G. D.; Vostrova, N. G.; Stepanova, L. G.; Avakova, A. N. *Dokl Akad Nauk SSSR* 247(6): 1498-1501; 1979.

An attempt was made to evaluate whether human cells infected with oncornavirus can repair the DNA breaks induced by the chemical carcinogen 4-nitroquinoline-1-oxide (4-NQO). Cultured diploid human cells (line T-9) infected with oncornavirus (strain LPV) were treated with 4-NQO (1×10^{-7} - 5×10^{-6} M) for 30 or 60 min; then cell lysates were centrifuged in sucrose gradient, and the number of breaks was determined from the mol wt of gradient fractions. It was found that noninfected and transformed cells were capable of repairing 4-NQO-induced DNA breaks (coefficient of repair, 90%-100%), while cells infected with LPV virus showed marked inhibition of DNA repair (coefficient of repair, 0%-52%). (9 refs)

- 79-6228 Mutagenicity Evaluation of the Two Antimalarial Agents Chloroquine and Mefloquine, Using a Bacterial Fluctuation Test. (Eng) Schupbach, M. E. (Biological and Pharmaceutical Res. Dept., F. Hoffmann-La Roche and Co., Ltd., Basel, Switzerland). *Mutat Res* 68(1): 41-49; 1979.

Two antimalarial agents, chloroquine diphosphate (7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline-diphosphate) and Mefloquine hydrochloride (2,8-bis-(trifluoromethyl-a-(2-piperidyl)-4-quinolinemethanol hydrochloride) were tested for mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 by a fluctuation test. Chloroquine reverted strain TA1537 without metabolic activation at concentrations of 100 and 250 $\mu\text{g/ml}$, probably by intercalation. No mutagenicity was found with mefloquine at concentrations of 0.5-2.4 $\mu\text{g/ml}$, with or without metabolic activation. Concentrations above 2.5 $\mu\text{g/ml}$ inactivated the bacteria and could not be tested. The high correlation between mutagenicity and carcinogenicity makes it likely that chloroquine is carcinogenic. Because of the mutagenic and probably carcinogenic risk of chloroquine and because of the increasing need for new antimalarial drugs, the existence of other antimalarial compounds, eg, mefloquine, which do not bind to DNA, should be stressed. (26 refs)

- 79-6229 Endocytosis and Chloroquine Accumulation During the Cell Cycle of Hepatoma Cells in Culture. (Eng) Quintart, J. (Laboratoire de Chimie Physiologique, Université de

CHEMICAL CARCINOGENESIS

Louvain, Louvain, Belgium); Leroy-Houyet, M. A.; Trouet, A.; Baudhuin, P. *J Cell Biol* 82(3): 644-653; 1979.

Endocytosis in hepatoma tissue culture (HTC) cells was studied by following the accumulation of horseradish peroxidase (HRP), radiolabeled dextran, and chloroquine. In asynchronously growing cells exposed for 1 hr to 5 mg/ml peroxidase, HRP uptake was linear for at least 3 hr. In synchronized cells, the accumulation was lowest at mitosis and increased during the first hours of the G1 phase. Between 16-20 hr after mitosis, accumulation decreased. A similar pattern was observed for the uptake of dextran (0.5 or 1 mg/ml). Dextran was largely recovered in soluble form upon homogenization, and its transfer to lysosomes was much slower than that of peroxidase. It is postulated that a significant portion of the dextran is adsorbed to the pericellular and phagosomal membranes, which results in the slow transfer into lysosomes. The variation in dextran uptake during the cell cycle probably reflects changes in both the adsorptive properties of the pericellular membrane and in the endocytic uptake rate. The kinetics of accumulation of chloroquine in synchronously growing HTC cells were also nonlinear. It was taken up more rapidly during G1 and S, while accumulation was lowest in mitotic cells. Since chloroquine uptake is an indirect way of measuring the pH and buffering capacity of lysosomes, the observations indicate that these properties vary in parallel with changes in endocytic properties during the cell cycle. It is concluded that actively dividing cells in culture are capable of regulating the processing of substances taken up from the surrounding medium, under the sole influence of intracellular events. No evidence for the intervention of lysosomes in mitosis was obtained. (41 refs)

79-6230 Adenine N⁶-Substituent of Agrocins 84 Determines its Bacteriocin-like Specificity. (Eng) Tate, M. E. (Waite Agricultural Res. Inst., Univ. Adelaide, Glen Osmond, S. Australia 5064); Murphy, P. J.; Roberts, W. P.; Kerr, A. *Nature* 280(5724): 697-699; 1979.

Structural determinants of the bacteriocin-like specificity of agrocins 84 (the active factor in the biological control of crown gall, a plant cancer induced by certain strains of *Agrobacterium*) were studied. For the pathogenic strain 57A, agrocins 84 was 360-fold more potent than its nucleotide fragment. However, the non-pathogenic strain 57 was inhibited by the nucleotide degradation fragment but not by agrocins 84 at a similar range of molarities. Thus, the nucleotide fragment without the N⁶-D-glucosylphosphoramidate substituent showed the nonspecific growth inhibition of a simple antibiotic, whereas only agrocins 84 with its unusual N⁶ substitution showed the strain specificity of a bacteriocin for the pathogenic strain 57A. For detectable antibiotic activity, a phosphoramidate linkage at the amphiphilic 2,3-dihydroxy-4-methylpentanamide appeared to be mandatory. The pathogenic in planta transconjugant strain 57A was originally obtained using the nonpathogenic strain 57 as the recipient and the pathogenic strain 27 as donor. Strain 57A differed from strain 57 solely by the presence of an electrophoretic band corresponding in mobility to the 1.5 x 10⁶ mol wt donor strain 27 tumor inducing plasmid. (14 refs)

79-6231 Cyclic Nucleotide Concentrations in Asbestos-induced Rat Peritoneal Mesothelioma. (Eng) Stevens, R. H. (Radiation Res. Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA 52242); Will, L. A.; Cole, D. A.; Meek, E. S.; Frank, C. W.; Donham, K. J. *Environ Res* 19(2): 442-448; 1979.

The roles of cyclic AMP (cAMP) and cyclic guanosine monophosphate (cGMP) in the development and growth of asbestos-induced peritoneal mesotheliomas in the rat were determined. Peritoneal mesotheliomas were induced through the ip administration of Rhodesian chrysotile "A" to weanling male Holtzman rats. The intracellular concentrations of cAMP and cGMP were significantly less than the levels measured in comparable control tissues obtained from age-matched animals that had been similarly administered charcoal instead of the asbestos. The calculated molar ratio of cAMP to cGMP was identical in tumors and control tissue, implying that the two cyclic nucleotides were diminished by a constant factor in the tumor tissue. However, if tumorigenesis is related to the cAMP/cGMP balance within the cancer cell, then in these apparently noninvasive lesions such an equilibrium exists as is found in cells of normal mesentery. These results indicate that asbestos-induced mesotheliomas are similar to other cancerous tissues of the digestive tract in that they contain less of the adenosine cyclic nucleotide than the normal tissue. The findings suggest the possible loss of important cellular regulatory mechanisms in tumors induced by an important environmental carcinogen. (20 refs)

79-6232 Induction of Reproductive System Tumors in Mice by N⁶-(Methylnitroso)-adenosine and a Tumorigenic Effect of Its Combined Precursors. (Eng) Anderson, L. M. (Walker Lab., Memorial Sloan-Kettering Cancer Center, Rye, NY 10580); Giner-Sorolla, A.; Greenbaum, J. H.; Last-Barney, K.; Budinger, J. M. *Int J Cancer* 24(3): 319-322; 1979.

N⁶-(Methylnitroso)adenosine [m⁶(NO)Ado] was given in the drinking water (1 millimolar soln) of noninbred Swiss mice from 3 wk of age until death. This treatment resulted in the appearance of primary lung tumors in 16/20 females and 13/19 males; this was a significantly greater tumor incidence than the 19% occurring in both male (4/21) and female (3/16) control mice. At least one reproductive system tumor was found in 18/20 m⁶(NO)Ado-exposed females, including mammary tumors in 12 and uterine tumors in 5. The precursors of m⁶(NO)Ado, N⁶-methyladenosine (m⁶Ado) and nitrite, did not elevate tumor incidence when given alone; but when administered together they induced lung tumors in 11/19 male mice compared to 4/21 controls. Exposure of the mice to the nitrosated base N⁶-(methylnitroso)adenine [m⁶(NO)A] caused a significant increase in the number of lung tumors in male mice (11/19). Mammary tumors occurred in three females given m⁶(NO)A. The tumorigenic effect of m⁶Ado plus nitrite implies in vivo (probably intragastric) formation of a carcinogen, probably m⁶(NO)Ado. (13 refs)

79-6233 Esophageal Carcinoma in the Rat Induced with Methyl-alkyl-nitrosamines. (Eng) Stinson, S. F. (Tumor Pathology Branch, NCI, NIH, Bethesda, MD 20014). *Am J Pathol* 96(3): 871-874; 1979.

The previously reported induction of esophageal neoplasms by N-methyl-N-benzyl nitrosamine (MBZN): 2.5 mg/kg, sc, 1x/wk x 20) in F344 rats is described. All treated animals developed neoplasms as early as 18-20 wk after the first injection. Sixty-six percent of the lesions were papillomas, 17% pedunculated papillary carcinomas, and 17% sessile carcinomas. Histologically, all neoplasms showed squamous differentiation. Most carcinomas that invaded the esophageal wall were characterized by prominent intraluminal proliferation of well-differentiated squamous cells in

a papillary arrangement. Deep penetration of the wall by anaplastic chords of poorly differentiated cells was common. Although the carcinomas were invasive, no metastasis to distant sites was observed. No proliferative or neoplastic changes were induced in other organs by MBZN. Squamous cell carcinoma is the most frequently observed type of human esophageal cancer. The human neoplasms are usually well-differentiated and are deeply invasive. Growth patterns are also similar in this rat model and human esophageal cancer. Although the predominant papillary form of esophageal neoplasm in the rat is rare in man, a few cases have been reported. It is concluded that this model will be useful for the study of human esophageal carcinoma. (9 refs)

- 79-6234 Differential Expression of α -Fetoprotein and γ -Glutamyltranspeptidase in Chemical and Spontaneous Hepatocarcinogenesis. (Eng) Jalanko, H. (Div. Immunology, City of Hope Natl. Medical Center, Duarte, CA 91010); Ruoslahti, E. *Cancer Res* 39(9): 3495-3501; 1979.

The expression of two markers of fetal liver, α -fetoprotein (AFP) and γ -glutamyltranspeptidase (GGT), was studied during spontaneous and o-aminazotoluene (AT)-induced carcinogenesis in female C3H/A/BOM mice and male C3HeB/FeJ mice (AT given as 0.006% of the diet). Elevated serum AFP was first observed 3 wk after commencement of AT feeding in the female C3H/A/BOM mice. This increase subsided and was followed by a sustained increase at 5 mo. After 8 mo of carcinogen feeding and 2.5 mo on a normal diet, grossly visible liver tumors were observed in 25/28 (89%) mice. The liver in all 25 cases was covered by 10-50 small nodules, and large hepatomas were present in 12 animals. Some small oval cells and scattered adult-type hepatocytes contained AFP during the early stage of chemical carcinogenesis. During the later phase, AFP was detected in a few of the nodular areas, in solitary hepatocytes, and in groups of carcinoma cells. Spontaneous hepatomas in male C3HeB/FeJ mice also contained AFP. Fetal rat liver contained 100- to 1,000-fold more GGT than adult liver. During AT carcinogenesis, a significant increase in GGT was evident within 1 wk; this increase preceded that of AFP. No increase in GGT activity was found in the spontaneous benign or malignant liver lesions, however. The results indicate that the production of AFP and GGT is not turned on as a single 'genetic package', and that these two markers differ in their behavior during liver carcinogenesis. (31 refs)

- 79-6235 Mutagenic Activation of 2,4-Diaminoanisole and 2-Aminofluorene In Vitro by Liver and Kidney Fractions from Aromatic Hydrocarbon Responsive and Nonresponsive Mice. (Eng) Aune, T. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); Dybing, E. *Biochem Pharmacol* 28(18): 2791-2797; 1979.

The mutagenicities of the two carcinogenic arylamines 2,4-diaminoanisole (2,4-DAA, 5-50 μ g) 2-aminofluorene (AF, 2-10 μ g) were compared using liver and kidney fractions from two aromatic hydrocarbon (3-methylcholanthrene, MC) responsive and two nonresponsive mouse strains. MC pretreatment (80 mg/kg ip) of mice caused an increase in 2,4-DAA mutagenicity with liver fractions from all four strains. Kidney fractions had very low basal 2,4-DAA mutagenic activity. MC treatment led to a 14- to 27-fold increase in 2,4-DAA mutagenicity in the responsive C57BL/6/BOM (B6) strain, but not in any of the other strains. AF mutagenicity was increased with liver fractions from all four mouse strains, to the greatest extent in the B6 mice. AF showed

high basal mutagenic activity with kidney fractions from all four strains, but MC treatment did not cause any increase in AF mutagenicity in any of the strains. Thus, there was a clear difference in the pattern of metabolic activation of the two arylamines by liver and kidney fractions in mice, both with respect to constitutive activities and the response to aromatic hydrocarbons. (18 refs)

- 79-6236 Changes in Polyamine Content During Hepatocarcinogenesis. (Eng) Nagarajan, B. (Cancer Inst., Madras-600 020, India); Sukumar, S. *Indian J Cancer* 15(4): 55-59; 1978.

Polyamine, polyamine biosynthesis enzyme, ornithine carbamyl transferase (OCT), arginase, and nucleic acid levels were studied in 3'-methyl-dimethylaminoazobenzene (3'-Me-DAB) carcinogenesis. Six-wk-old Wistar albino rats were fed a diet containing 3'-Me-DAB (600 mg/kg diet) for 90-100 days followed by 3-4 mo on stock diet. Animals were examined weekly for histological liver changes, and an attempt was made to correlate cell dedifferentiation with changes in the enzyme activities. Ornithine decarboxylase showed a gradual increase after the initiation of treatment and had almost doubled by the ninth wk. OCT and arginase activities gradually decreased after the start of treatment. As early as the first wk, OCT activity dropped to 50% of the normal liver level. The decrease in arginase activity was slower than that of OCT. There was a progressive increase in total liver DNA during the period of azo-dye feeding, but there was little change in the RNA level until the fourth wk, after which there was a slight decline. The DNA/RNA ratio of 0.22 rose to almost 1.0 by the 17th wk of DAB administration. The concentrations of putrescine, spermidine, and spermine all rose during DAB treatment. (10 refs)

- 79-6237 Detection by Antihapten Antibodies of Liver-bound Compounds Related to Azocarcinogens or Their Metabolites. (Eng) Carruthers, C. (Orchard Park Labs., Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY); Baumler, A.; Lin, J. K. *Oncology* 36(5): 211-215; 1979.

The localization of known azocarcinogens and metabolites bound to components of liver cells of male Fischer rats (CDF inbred strain) that received azo compounds by stomach tube was determined using antibodies raised against a number of these compounds in the indirect fluorescent antibody procedure. The rats received 3'-methyl-*p*-dimethylaminoazobenzene (3'-Me-DAB), *N*-methyl-*p*-aminoazobenzene (MAB), *p*'-amino-*p*-aminoazobenzene (*p*'-amino-*p*-AAB), or *p*'-amino-*N*-monomethyl-*p*-aminoazobenzene (*p*'-amino-*p*-MAB) at 20 mg/100 g body wt and sacrificed 17 or 41 hr (3'-Me-DAB-treated rats) later. Antisera raised against *p*-azo-*N*-acetyl-*N*-methylaniline (*p*-azo-AMA), azoaniline, *p*-azo-*N*-monomethylaniline, and *p*-azoazobenzene (*p*-AB) reacted in agar producing precipitin lines of identity with the cytosols prepared from the livers of rats fed each of the azo compounds. In the fluorescent antibody procedure, *p*'-azo-*N*-monomethyl-*p*-aminoazobenzene and *p*'-azo-*p*-aminoazobenzene antisera reacted strongly with liver cells of rats red 3'-Me-DAB or MAB, and *p*-AB antisera reacted strongly with liver cells of rats fed *p*'-amino-*p*-MAB, MAM, or *p*'-amino-*p*-AAB. These results suggest that both minor and major metabolites of azocarcinogens have common antigenic determinants and indicate that these metabolites are bound to liver cell components. (11 refs)

79-6238 Rubber Solvent: A Clastogenic Agent that Fails to Induce Sister-Chromatid Exchanges. (Eng) Altenburg, L. C. (Medical Genetics Center, Univ. Texas Health Science Center at Houston, Houston, TX 77025); Ray, J. H.; Smart, C. E.; Moore, F. B. *Mutat Res* 67(4): 331-341; 1979.

Rubber solvent (a mixture of paraffins, monocycloparaffins, monoolefins, benzene, and alkyl benzene) was tested for its ability to induce chromosome aberrations and sister chromatid exchanges (SCEs) in whole blood cultures from a normal human donor. The solvent proved to be a clastogenic agent for human whole blood, the highest concentration tested (0.0750%) producing at least a threefold increase in all types of chromosome aberrations. As the solvent concentration increased from 0%-0.750%, the number of cells showing one or more aberrations increased to a max of slightly over 50% of the cells. Chromosomal aberrations included gaps, chromatid breaks, and chromosome pulverization. There were no increases in SCE frequency at any of the solvent concentrations tested. The absence of increased SCE frequency in these cells suggests that DNA replication is not required for the induction of chromosomal aberrations by the clastogenic agent(s) in rubber solvent. (40 refs)

79-6239 Induction of Dominant Lethal Mutations in Male Mice by Fosfestrol. (Eng) Ehling, U. H. (Abteilung für Genetik der Gesellschaft für Strahlen und Umweltforschung, Ingolstädter Landstrasse 1, D-8042 Neuherberg, W. Germany). *Arch Toxicol* 42(3): 171-177; 1979.

The ability of fosfestrol, a diethylstilbestrol derivative, to induce mutations in male mice was tested and confirmed in a dominant lethal assay. With up to 300 mg/kg of fosfestrol, the induction of mutations occurred exclusively in spermatozoa. A dose of 600 mg/kg fosfestrol induced dominant lethal mutations up to 10 days posttreatment. In all dose groups, the majority of the induced dominant lethal mutations were expressed as losses after implantation. (15 refs)

79-6240 Carcinomas of the Liver in Female Mice Fed Toluene-2,4-diamine. (Eng) Reuber, M. D. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, P. O. Box B, Frederick, MD 21701). *Gann* 70(4): 453-457; 1979.

The hepatocarcinogenicity of toluene-2,4-diamine was tested in B6C3F1 mice fed 100 or 200 ppm in the diet for 100 wk. Females fed both doses of the aromatic amine developed significant numbers of liver carcinomas (39% of those fed 200 ppm, $p = 0.00093$; 30% of those fed 100 ppm, $p = 0.00010$), and these included both well differentiated and poorly differentiated tumors. Treated mice also developed hyperplastic hepatic nodules, but cirrhosis was not observed. The incidence of hepatic neoplasms (carcinomas + hyperplastic nodules) was significant ($p \leq 0.00001$) in female mice. Hyperplastic nodules, carcinomas, and liver cirrhosis have been previously described in rats fed toluene-2,4-diamine. (16 refs)

79-6241 Chemical Studies on Tobacco Smoke LXIV. On the Analysis of Aromatic Amines in Cigarette Smoke. (Eng) Patrianakos, C. (Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Hoffmann, D. *J Anal Toxicol* 3(4): 150-154; 1979.

An analytical method for aromatic amine profiles in cigarette smoke was developed, and a comparative study of aromatic amines in various tobacco products was carried out. Amines from smoke are trapped in dilute hydrochloric acid and are enriched together with the basic portion, derivatized to pentafluoropropionamides and determined by gas chromatography with a ^{63}Ni -electron capture detector (detection limit 50 pg aniline/cigarette). The mainstream smoke of one US 85-mm cigarette without filter tip contained 102 ng of aniline, 61 ng of 2-toluidine, 3-toluidine, and 4-toluidine, 55.8 ng of ethylaniline and dimethylaniline, 4.3 ng of 1-naphthylamine, 6.9 ng of 2-aminobiphenyl, 3-aminobiphenyl, and 4-aminobiphenyl, and 5.8 ng of 2-methyl-1-naphthylamine. Sidestream smoke contained levels of aromatic amines 20 to 68 times higher than those in the mainstream smoke. The results from smoke analyses of experimental cigarettes support the concept that the nitrate and protein content of tobacco are determining factors for the smoke yields of aromatic amines. (21 refs)

79-6242 Collaborative Studies on the Salmonella/Microsome Mutagenicity Assay. (Eng) Dunkel, V. C. (NCI, NIH, Bethesda, MD 20014). *J Assoc Off Anal Chem* 62(4): 874-882; 1979.

A collaborative study was undertaken to determine the reproducibility of results obtained with the Salmonella/microsome mutagenicity assay. Three laboratories tested 61 carcinogens and noncarcinogens with and without metabolic activation using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100. The metabolic activation systems were derived from the livers of uninduced and Aroclor 1254-induced Fischer rats, B6C3F₁ mice, and Syrian hamsters. Eight of 23 chemicals were negative and 13 were positive when tested by all three laboratories. Two chemicals, 2-methyl-4-dimethylaminoazobenzene and parosanol, were positive according to two laboratories and negative according to the third. There was complete agreement among laboratories with regard to overall negative responses. Except for the two compounds mentioned, all laboratories obtained positive responses with activation-dependent chemicals in at least one activation system. Species variation was observed in the ability of the S-9 mix to metabolize chemicals to active mutagens; in each case, there was increased activity with the hamster preparations. In general, better responses were obtained with enzyme preparations from induced animals than with those prepared from uninduced animals. (3 refs)

79-6243 Genetic Toxicity of Procarbazine in Bacteria and Yeast. (Eng) Bronzetti, G. (Lab. Mutagenesi e Differenziamento, Via Cisanello 147B, Pisa, Italy); Zeiger, E.; Malling, H. V. *Mutat Res* 68(1): 51-58; 1979.

Procarbazine [*N*-isopropyl- α -(2-methylhydrazino) - *p*-toluamide hydrochloride], used to treat Hodgkin's disease, was tested in vitro with and without the S10 fraction from mice liver (microsomal assay) using *Saccharomyces cerevisiae* strain D₁, *Salmonella typhimurium* (strains TA98, TA100, TA1535), and in vivo in Swiss albino mice (host-mediated assay) using D₁. Procarbazine, without S10 fraction, was highly toxic and induced mitotic crossover, gene conversion, and reverse mutation in D₁ at all doses tested in vitro [17, 34, or 68 mg/ml]. It had a toxic effect on all the *Salmonella* strains at concentrations ranging from 10-100 mg/ml, but did not induce reverse mutations at the histidine loci. Procarbazine with S10 fraction was less toxic and did not induce genetic effects in

yeast or *Salmonella*. In the host-mediated assay, no genetic effects were seen. (34 refs)

- 79-6244 Oxidative Metabolism of *N*-Isopropyl- α -(2-methylhydrazino)-*p*-toluamide Hydrochloride (Procarbazine) by Rat Liver Microsomes. (Eng) Dunn, D. L. (Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX 75235); Lubet, R. A.; Prough, R. A. *Cancer Res* 39(11): 4555-4563; 1979.

The oxidative metabolism of procarbazine (*N*-isopropyl- α -(2-methylhydrazino)-*p*-toluamide hydrochloride) by rat liver microsomes was studied utilizing three different biochemical assays. Using high-pressure liquid chromatography, it was observed that the major stable microsomal metabolite produced was the azo derivative, *N*-isopropyl- α -(2-methylazo)-*p*-toluamide, which was able to undergo a rapid chemical conversion to the aldehyde *p*-formyl-*N*-isopropylbenzamide and methylhydrazine upon the addition of acid. The rate of metabolism could most conveniently be determined spectrophotometrically by reacting the resultant methylhydrazine with *p*-dimethylaminobenzaldehyde. Alternately, *p*-formyl-*N*-isopropylbenzamide could be extracted directly from the acid-treated mixture with an organic solvent, and its concentration could be determined spectrophotometrically. Rates of metabolism using all three assays ranged from 13.4-14.1 nanomoles/min/mg of microsomal protein. Inhibitor and induction studies indicated that the cytochrome P-450-dependent monooxygenase system is responsible for this oxidation reaction. Several possible mechanisms were considered: either a direct dehydrogenation of a preliminary *N*-oxidation by cytochrome P-450 followed by a rapid dehydration step. The azo derivative of procarbazine was further oxidized to two isomeric azoxy derivatives, *N*-isopropyl- α -(2-methyl-NNO-azoxy)-*p*-toluamide and *N*-isopropyl- α -(2-methyl-ONN-azoxy)-*p*-toluamide, at a metabolic rate which was 10-15% as great as the rate of procarbazine oxidation. In addition, the affinity of the azo derivative for the monooxygenase was high relative to that of the parent hydrazine. The reaction was inhibited by cytochrome P-450 inhibitors and was sensitive to the *in vitro* addition of several thionosulfur-containing compounds. The azoxy compounds were also metabolized by microsomal fractions from liver and yielded *p*-formyl-*N*-isopropylbenzamide as a product. This complex *in vitro* metabolic scheme is analogous to the *in vivo* metabolism of 1,2-dimethylhydrazine and suggests that procarbazine may be metabolically activated to yield alkylating agents capable of expressing carcinogenic and/or toxic effects by a mechanism common to at least these two *N,N'*-disubstituted hydrazines. (43 refs)

- 79-6245 Accelerating Effect of Ascorbic Acid on *N*-Nitrosamine Formation and Nitrosation by Oxyhyponitrite. (Eng) Chang, S. K. (Johnson and Johnson Co., New Brunswick, NJ); Harrington, G. W.; Rothstein, M.; Shergalis, W. A.; Swern, D.; Vohra, S. K. *Cancer Res* 39(10): 3871-3874; 1979.

The reaction of nitrite ion with ascorbic acid and its effect on the rate of nitrosation of secondary amines were investigated using differential pulse polarography in aqueous acidic solution. Ascorbic acid showed nonuniform behavior: it accelerated the nitrosation of *N*-methylaniline between pH 1.00 and 1.95, allowed the nitrosation of diphenylamine and iminodiazetonitrile, and inhibited the nitrosation of secondary amines such as

dimethylamine, diethylamine, proline, hydroxyproline, *N*-methylaminoacetonitrile, *N*-methylaminopropionitrile, and sarcosine. The three amines that were nitrosated were relatively weak bases, whereas those that were not were relatively strong. The nitrosating agent generated by the reaction between ascorbic acid and nitrite ion appeared to be oxyhyponitrite ion. The addition of ascorbic acid to a commercial product containing a variety of unknown amines might slow down the formation of some nitrosamines but accelerate the formation of others, which might generate more potent carcinogens by transnitrosation. (32 refs)

- 79-6246 The *N*-Hydroxy Metabolites of *N*-Methyl-4-aminoazobenzene and Related Dyes as Proximate Carcinogens in the Rat and Mouse. (Eng) Miller, E. C. (McArdle Lab. Cancer Res., Univ. Wisconsin Center Health Sciences, Madison, WI 53706); Kadlubar, F. F.; Miller, J. A.; Pitot, H. C.; Drinkwater, N. R. *Cancer Res* 39(9): 3411-3418; 1979.

The carcinogenicities for rats and mice of the dye *N*-methyl-4-aminoazobenzene (MAB) and its hepatic microsomal metabolite *N*-hydroxy-*N*-methyl-4-aminoazobenzene (*N*-hydroxy-MAB) were compared under several conditions. The related dyes *N*-ethyl-4-aminoazobenzene (EAB), 4-aminoazobenzene (AB), and their *N*-hydroxy derivatives were also included in some of the assays. About 25% of the rats given MAB or *N*-hydroxy-MAB (3-5 millimoles/kg) by stomach tube over a 5-wk period developed hepatic tumors by 18-22 mo. Similarly treated rats subsequently given phenobarbital in the drinking water until the termination of the experiment developed about twice as many hepatic tumors. *Pro* administration of *N*-hydroxy-MAB, but not MAB, also induced multiple papillomas and extensive carcinomas of the forestomach in approx 50% of the rats. Only low incidences of hepatocellular carcinomas occurred in partially hepatectomized rats given a single ip injection of 180 micromoles of MAB or *N*-hydroxy-MAB with or without subsequent administration of phenobarbital. Although repeated sc doses of *N*-benzoyloxy-*N*-methyl-4-aminoazobenzene induced sarcomas at the injection site in 90% of the rats, only 3/20 rats developed sarcomas at the site of sc injections of *N*-hydroxy-MAB. EAB, AB, and their *N*-hydroxy derivatives did not induce significant numbers of tumors in any of the above assay systems. Administration to preweanling male mice of MAB, *N*-hydroxy-MAB, *N*-hydroxy-EAB, and *N*-hydroxy-AB resulted in high incidences and high multiplicities of hepatic tumors (av of 5-7 tumors/mouse) within 1 yr. EAB and AB also induced hepatic tumors under the same conditions, but they were less active. The data support the conclusion that the *N*-hydroxy metabolites of these aminoazo dyes are proximate carcinogens. (46 refs)

- 79-6247 Binding of the Chemical Carcinogen, *p*-Dimethylaminoazobenzene, by Human Plasma Low Density Lipoproteins. (Eng) Chen, T. C. (Dept. Biochemistry, Methodist Hosp., Baylor Coll. Medicine, Houston, TX 77030); Bradley, W. A.; Gotto, A. M.; Morrisett, J. D. *FEBS Lett* 104(2): 236-240; 1979.

p-Dimethylaminoazobenzene (phenyl-¹⁴C; ¹⁴C-DAB) was incubated with 1 ml of whole blood from normal male and female donors, plasma lipoprotein soln, or albumin soln for 6 hr. In experiments using whole blood, 15% of the radioactivity was distributed into cellular components, while the remainder was bound to the lipoproteins and lipid-free plasma proteins. When the three principal classes of lipoproteins [low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density

lipoproteins (VLDL)] were separated by agarose gel filtration chromatography, 77% of the incorporated ^{14}C -DAB was associated with LDL, 10% with VLDL, and 13% with HDL. Incubation of ^{14}C -DAB (at a subsaturating level) with LDL and albumin present at a normal physiological ratio resulted in the distribution of 88% of the radioactivity into the LDL and 12% into the albumin fraction. This study does not establish the actual binding site(s) for the DAB but suggests that it may be bound at the hydrophobic core of the lipoproteins. Specific receptor sites for LDL exist in a variety of normal cells. If LDL is the major transport vehicle for water-insoluble carcinogens in vivo, then transfer of the carcinogens from LDL to these normal cells might cause neoplastic transformation if the accessible cells possess the necessary enzyme systems for carcinogenic metabolic activation. (25 refs)

- 79-6248 Recessive Lethals Induced by Styrene and Styrene Oxide in *Drosophila melanogaster*. (Eng) Donner, M. (Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Helsinki, Finland); Sorsa, M.; Vainio, H. *Mutat Res* 67(4): 373-376; 1979.

The induction of recessive lethal mutations in phenobarbitone (PB)- or trichloropropane (TCP)-pretreated *Drosophila melanogaster* by styrene (200 ppm) and styrene oxide (SO: 200 ppm) was studied. The compounds were administered by feeding for 24 hr or inhalation for 6 hr/day over 4 consecutive days. In the feeding experiments, styrene was slightly more toxic than SO (LC_{50} approx 500 and 700 ppm, respectively). Neither PB nor TCP alone was mutagenic, but both increased the production of recessive lethals by styrene or SO by approx twofold. Styrene or SO alone significantly increased the number of recessive lethals over control rates. The increased yield of recessive lethals after combined treatment with PB plus styrene can be explained on the basis of an enhancement of the conversion of styrene to epoxide derivative(s). It is possible that further oxidation of styrene-7,8-oxide might take place at the 3,4-position of the aromatic ring, and this metabolic pathway could be stimulated by PB treatment in *Drosophila*. This mechanism could explain the enhanced mutagenicity of SO after PB treatment. (12 refs)

- 79-6249 Induction of Enzyme Activity in Cell Culture: A Rapid Screen for Detection of Planar Polychlorinated Organic Compounds. (Eng) Bradlaw, J. A. (Div. Toxicology, Food and Drug Admin., Washington, DC 20204); Casterline, J. L. *J Assoc Off Anal Chem* 62(4): 904-916; 1979.

The detection of planar polychlorinated organic compounds by the cell culture-enzyme induction bioassay is described. Aryl hydrocarbon hydroxylase (AHH) activity was measured by the conversion of benzo(a)pyrene (BP) to 3-hydroxy-BP in homogenized cell extracts from control and treated cultures. Substances screened by this method included polyhalogenated analogs of dibenzo-p-dioxin (24 compounds), dibenzofuran (11), biphenyl (7), and extracts from several food sources. The response of the most reactive compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin, was used to prepare a standard curve, and the AHH activity induced by mole doses of each test substance was reported as an ED_{50} response (the estimated dose needed to produce 50% of max enzyme induction). A potent ED_{50} response in cell culture appeared to correlate well with known toxic responses in other mammalian and avian systems for certain test substances. This correlation suggests that the cell culture-enzyme induction method is a

useful model for screening food extracts that are suspected of being contaminated with polychlorinated planar substances. (31 refs)

- 79-6250 An Estimate of the Maximum In Vivo Covalent Binding of 2,3,7,8-Tetrachlorodibenzo-p-dioxin to Rat Liver Protein, Ribosomal RNA, and DNA. (Eng) Poland, A. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Glover, E. *Cancer Res* 39(9): 3341-3344; 1979.

In light of the recently discovered potent carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female rats, the in vivo covalent binding of ^3H TCDD to rat liver macromolecules was reexamined. Immature Sprague-Dawley rats, receiving ^3H TCDD (0.87 mCi/kg; specific activity, 39 Ci/millimole) concentrated 18%-64% of the total administered dose in their livers, but virtually all of this radioactivity (>99.9%) was extractable. The max unextractable radioactivity was: protein, 60 picomoles (pmol) TCDD/mole (mol) of amino acid residue; ribosomal RNA, 12 pmol TCDD/mol of nucleotide residue; and DNA, 6 pmol TCDD/mol of nucleotide residue. If one assumes that this small residual amount of radioactivity represents covalent binding, this binding is four to six orders of magnitude lower than that of most chemical carcinogens, and the binding to DNA is equivalent to one molecule of TCDD per DNA, equivalent to 35 cells. The results suggest that it is unlikely that TCDD-induced oncogenesis is through a mechanism of covalent binding to DNA and somatic mutation. (29 refs)

- 79-6251 Carcinogenic Properties of Dicarboxydine (γ,γ' -3,3'-benzidine dioxydibutyric Acid). (Eng) Pliss, G. B. (Lab. Chemical Carcinogenic Agents, Petrov Res. Inst. Oncology, 68 Leningradskaya St., Pesochny-2, Leningrad 188646, USSR); Volfson, N. I. *Arch Geschwulstforsch* 49(3): 229-239; 1979.

The carcinogenicity of dicarboxydine (DCD) for male and female rats (35 or 45 mg/wk DCD, sc for 24 mo or 20 mg DCD po 5 days/wk for 24 mo) and male and female CC₅₇Br mice (3 or 4 mg/wk, sc or 3 mg/day po 5 days/wk) was studied. The percentages of tumors developing in the treated rats was 13.6% in the low-dose sc group, 26.2% in the high-dose sc group, and 28.6% in the po group, as compared with 19% in a control group. The latent periods of tumor development did not differ significantly between DCD and control groups. Four DCD-treated rats developed sarcomas at the injection site and others developed tumors of the bladder, prostate, uterine body, and other sites; tumors of these sites were not found in the control rats. DCD showed no significant tumorigenic activity in the mice. The results suggest that DCD possesses low carcinogenic activity. (9 refs)

- 79-6252 Genetic Effects of Impure and Pure Saccharin in Yeast. (Eng) Moore, C. W. (Dept. Radiation Biology and Biophysics, Univ. Rochester, Rochester, NY 14642); Schmick, A. *Science* 205(4410): 1007-1010; 1979.

The effects of pure and impure saccharin on mitotic and intragenic recombination and reverse mutation in *Saccharomyces cerevisiae* were studied, and the extents to which these genetic events are affected by impure saccharin produced by two different processes were compared. The diploid strain CM-1293 of *S. cerevisiae* was

incubated in medium containing 0, 2, or 20 mg of saccharin A (impure Maumee process saccharin), B (impure Remsen-Fahlberg process), or C (purified from the same B batch). Dose-dependent increases were observed in the frequencies of abnormal cells. The frequency of aberrant types was saccharin A > saccharin B > saccharin C. Such aberrant cell types were not observed in cultures grown in medium without saccharin. Intergenic exchanges between homologous chromosomes were 11-12 times more frequent in cells grown in the presence of the lowest dose of impure saccharins than in cells grown without saccharin. Half as many exchanges occurred among cells grown with the low dose of saccharin C. At all three concentrations, cells grown in the presence of saccharin B showed higher frequencies of mitotic crossing over or gene conversion than cells grown in saccharin C. Saccharin A usually caused larger increases in both recombination and mutation than saccharins B and C, indicating the greater potential mutagenicity of saccharin A. It is concluded that the impurities in saccharin caused some or all of the observed genetic effects. However, the impurities would have to be potent to account for all the effects of saccharin and, therefore, saccharin per se or its metabolites might cause the effects. (19 refs)

- 79-6253 Saccharin Metabolism and Tumorigenicity. (Eng) Sweatman, T. W. (Clinical Pharmacology Group, Univ. Southampton, Medical and Biological Sciences Bldg., Southampton SO9 3TU, England); Renwick, A. G. *Science* 205(4410): 1019-1020; 1979.

Adult male Charles River CD1 rats that had been exposed to saccharin in utero and maintained on a 5% saccharin diet were given free access to a diet containing 5% [³H]saccharin for 24 hr and then returned to the unlabeled diet (pulsed-dose experiment). In another experiment, normal rats received a single dose of [³H]saccharin (60 µg/kg) by intubation or 3-methylcholanthrene (MCA: 20 mg/kg, po) 3 and 2 days before a single dose of [³H]saccharin (400 µg/kg, po). The ³H label was eliminated, largely in the urine, within 48 hr. In the pulsed-dose experiment, fecal excretion was 14%, while in the two other experiments, fecal excretion was 2.5%-3% in rats given the 60 µg/kg dose and 6.5%-8% in rats treated with MCA and 400 µg/kg saccharin. Urine samples obtained 0-24 hr after labeled saccharin administration in the pulsed-dose experiment contained 98.5% saccharin and <0.05% 2-sulfamoylbenzoic acid. Similar results were obtained in the untreated rats given 60 µg/kg saccharin. These results demonstrate that significant metabolism is not induced by long-term saccharin administration during the neonatal and weaning stages of two-generation studies. The possibility that the carcinogenic effects of saccharin are due to the unmetabolized parent compound, to a promoting effect, or to changes in physiological function should be investigated. (11 refs)

- 79-6254 Genetic Effects of Hydralazine. (Eng) Shaw, C. R. (Dept. Biology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Butler, M. A.; Thenot, J. P.; Haegle, K. D.; Matney, T. S. *Mutat Res* 68(1): 79-84; 1979.

Hydralazine and its acetone condensation product were found to induce base-pair substitution mutations in the Salmonella/microsomal activation test system and to display genetic toxicity in the PolA⁺/A⁻ test system. A dose-response relationship was noted for mutagenicity of both compounds tested at doses up to 1,000 µg/plate. Incubation with a rat liver microsomal fraction did not

affect the genetic toxicity of either compound. Other derivatives of hydralazine, including the major metabolite 3-hydroxy-methyl-5-triazolo-[3,4a]phthalazine (MTP), did not yield any evidence of genetic toxicity, nor were they metabolically convertible to a toxic product. Therefore, individuals who convert hydralazine to MTP slowly, ("slow acetylators") would be expected to be at risk. (14 refs)

- 79-6255 Acute Leukemia After Azathioprine Therapy of Chronic Aggressive Hepatitis. (Ger) Krieger, G. (I. Medizinische Klinik, Städtisches Klinikum, Maltkestrasse 14, 7500 Karlsruhe 1, W. Germany); Keller, P.; Schirmeister, J. *Therapiewoche* (36): 5554-5555, 5558; 1979.

The case report of a 26-yr-old man who developed acute leukemia after receiving azathioprine (AZP: av dose, 150 mg/day) for 6 yr as treatment for chronic aggressive hepatitis is presented together with a literature review. Fluocortolone (Ultralan) was given briefly at 100 mg/day in 1969 and at 200 mg/day (shock therapy) in 1972. AZP was discontinued during fluocortolone therapy. The patient presented with leg pain, night sweats, and inguinal swelling, and rapidly developed an acute transverse-lesion syndrome. After brief improvement during chemotherapy, he died of heart failure, which was considered to be a result of leukemia. Autopsy showed massive infiltration of the lymphatic organs, liver, bone marrow and meninges with paramyeloblasts. Evidence of chronic aggressive hepatitis and the development of fibrosis was seen. Australia antigen was present in the serum at the time of the first diagnosis of hepatitis. Two reports of myeloid leukemia in patients treated with azathioprine were found in the literature, although neither patient had received alkylating agents. In other studies of 7,100 patients who received AZP for nonmalignant disease, no increased tumor incidence was observed. No increased tumor incidence was seen in 125 patients followed for 4 yr after treatment with azathioprine (100 mg/day) for an av of 2 yr. (29 refs)

- 79-6256 Activity of Citrinin Metabolized by Rat and Human Microsome Fractions in Clastogenicity and SCE Assays on Chinese Hamster V79-E Cells. (Eng) Thust, R. (Res. Group Preventive Oncology, Inst. Pathology Medical Acad. Erfurt, Nordhauser Strasse 74, DDR-50 Erfurt, E. Germany); Kneist, S. *Mutat Res* 67(4): 321-330; 1979.

The ability of the mycotoxin citrinin to induce chromosome aberrations and sister chromatid exchanges (SCE's) in Chinese hamster V79-E cells was investigated. In a clastogenicity assay, citrinin was a potent inducer of chromosome aberrations in the V79-E cells when metabolized by rat and human liver microsomes. Both types of microsomes, standardized with respect to protein content, activated citrinin at equal levels. At 5×10^{-4} M citrinin induced a high frequency of complex translocations as well as defects in chromosomal coiling. Higher concentrations were cytotoxic, lower ones almost inactive. After metabolization of the mycotoxin by rat kidney microsomes or an S9 mix fraction containing rat liver and kidney microsomes, toxic effects predominated and chromosome aberrations were diminished. Clastogenic citrinin concentrations did not increase the SCE frequency. Although the mode of action of this mycotoxin on chromosome structure remains obscure, several possible explanations are offered. (22 refs)

- 79-6257 Inhibitory Effects of Carcinogenic Mycotoxins on Deoxyribonucleic Acid-Dependent Ribonucleic Acid Polymerase and Ribonuclease H. (Eng) Tashiro, F. (Dept. Tox-

icology and Microbial Chemistry, Tokyo Univ. Science, Ichigaya, Shinjuku-ku, Tokyo 162, Japan); Hirai, K.; Ueno, Y. *Appl Environ Microbiol* 38(2): 191-196; 1979.

Fourteen mycotoxins were tested for in vitro inhibitory effects on RNA polymerase of rat liver and *Escherichia coli* and nuclear ribonuclease H of rat liver and *Tetrahymena pyriformis*. Both enzymes were strongly inhibited by (-)-luteoskyrin, (+)-rugulosin, patulin, and PR toxin. (+)-Rugulosin behaved like actinomycin D, which binds with DNA and inhibits RNA synthesis. Luteoskyrin selectively inhibited RNA synthesis by isolated rat liver nuclei and by RNA polymerases of rat liver, but not by RNA polymerases of *E. coli*. PR toxin inhibited RNA synthesis by both animal and bacterial RNA polymerases. The initiation, as well as the elongation reaction, of RNA polymerase I of rat liver was impaired by PR toxin, but with RNA polymerase II, PR toxin affected preferentially the initiation reaction. Rat liver ribonuclease H was inhibited by (-)-luteoskyrin, (+)-rugulosin, patulin, penicillic acid, and PR toxin. *O*-acetylsterigmatocystin and chlorocephalid did not inhibit in vitro RNA synthesis. Recovery from patulin-induced ribonuclease H inhibition in the presence of DDT, taken together with the results of previous experiments, supports the authors' proposal that patulin, penicillic acid, and PR toxin act as sulfhydryl group blockers with both ribonuclease H and RNA polymerase. (32 refs)

79-6258 Black Pepper [*Piper nigrum*]: Evidence of Carcinogenicity. (Eng) Concon, J. M. (Dept. Nutrition & Food Science, Univ. Kentucky, Lexington, KY 40506); Newburg, D. S.; Swerczek, T. W. *Nutr Cancer* 1(3): 22-26; 1979.

An extract of black pepper was applied cutaneously to albino Swiss mice of both sexes; each animal received a total of 28 mg over a 3-mo period. All pepper-treated mice surviving after 17 mo developed tumors, particularly in the lung, liver, and skin (distant from the area of application). The incidence of malignant tumors and of multiple tumors was significantly greater in the pepper-treated mice than in the vehicle-treated controls. (38 refs)

79-6259 Carcinomas and Other Lesions of the Liver in Mice Ingesting Organochlorine Pesticides. (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD 21701). *Toxicol Annu* 3: 231-256; 1979.

The induction and histopathology of carcinomas of the liver and other lesions in mice of various strains fed organochlorine pesticides were studied. A high incidence of well-, moderately well-, and poorly differentiated hepatocellular and cholangiocellular carcinomas was observed in mice given dieldrin, aldrin, heptachlor, heptachlor epoxide, kepone, lindane, chloroform, chlordane, or carbon tetrachloride. Increased incidences were also seen after the ingestion of chlorobenzilate, mirex, DDT, methoxychlor, or endrin. Hemangioendothelial sarcomas, leiomyosarcomas, and reticulum cell sarcomas were rarely seen in the livers of the pesticide-treated mice. Hyperplastic nodules were frequently observed in the livers of mice with and without liver tumors. There were occasional metastases to the lungs, the metastatic carcinomas being predominantly hepatocellular. Focal necrosis was occasionally seen in the treated mice, particularly those given heptachlor or heptachlor epoxide. Severe cirrhosis was observed in most animals given large doses of chloroform or carbon tetrachloride. (78 refs)

79-6260 Evaluation of Benzidine by the Micronucleus Test. (Eng) Cihak, R. (Res. Inst. Organic Syntheses, Pardubice-Rybitvi, Rosice, 533 51, Czechoslovakia). *Mutat Res* 67(4): 383-384; 1979.

Benzidine (100-300 mg/kg) and its derivative, 3,3'-dimethylbenzidine (DMB, 50-200 mg/kg) were tested for their mutagenicity using the micronucleus test in male Wistar rats. The compounds were administered by stomach tube 30 min and 6 hr before preparation of bone marrow smears. Both compounds significantly increased the frequency of micronucleated polychromatic RBC at all doses tested, but a dose-response relationship was observed only for DMB. The efficiency of the micronucleus test for the detection of carcinogens appears to be low, even when an appropriate experimental protocol is followed. (5 refs)

79-6261 Non-Mutagenicity of the Hair Dye, Henna, in the Ames Test. (Eng) Stamberg, J. (Dept. Microbiology, Faculty Life Sciences, Tel Aviv Univ., Ramat Aviv, Israel); Werczberger, R.; Koltin, Y. *Mutat Res* 62(2): 383-387; 1979.

The mutagenicities of henna and lawsone (2-hydroxy-1,4-naphthoquinone, the active coloring and medicinal ingredient in henna) for five histidine-requiring *Salmonella typhimurium* strains and the human epithelial AV3 cell line were studied. Henna at 0.2-1,000.0 µg/plate was not mutagenic for *S. typhimurium* strains TA1538, TA1537, TA1535, TA100, or TA98 (with and without metabolic activation with S9 mammalian-microsome fraction); it was mutagenic only for strain TA98 at concentrations ≥500 µg/plate and in the absence of S9 mix; in this case, there was a four- to sevenfold increase in reversion. Henna was toxic for *Salmonella* strains and *Ustilago maydis*, but there was no clear dose-response to henna or lawsone in either organism. Henna was toxic for human AV3 cells at doses >2 mg/ml. Five of six female C3H or C57BL mice given im injections of henna (5.0 mg/mouse) died within 11 days. ICR and BALB/c mice survived im injections of 5.0 or 10.0 mg/mouse. Topical application of henna (50 mg/mouse in three serial applications) in ICR and BALB/c mice produced neither death nor external malignancies after 9 mo of observation. (13 refs)

79-6262 Carcinogenicity and Nephrotoxicity of 2-Amino-, 1-Amino-2-methyl-, and 2-Methyl-1-nitro-anthraquinone. (Eng) Murthy, A. S. (EG&G Mason Res. Inst., Worcester, MA 01608); Russfield, A. B.; Hagopian, M.; Monson, R.; Snell, J.; Weisburger, E. K. *Toxicol Lett* 4(2): 71-78; 1979.

The carcinogenicity and nephrotoxicity of three cyclic dye intermediates, 2-aminoanthraquinone (AA), 1-amino-2-methylanthraquinone (1-Am-2-MeA), and 2-methyl-1-nitroanthraquinone (2-Me-1-NA), were determined in Fischer 344 rats and B6C3F₁ mice. The rats were fed 1.0% or 2.0% AA in the diet, 0.12% or 0.24% 1-Am-2-MeA, or 0.06% or 0.12% 2-Me-1-NA; the mice were fed 0.5% or 1.0% AA, 0.03% or 0.06% 1-Am-2-MeA, or 0.03% or 0.6% 2-Me-1-NA. In rats, all three chemicals increased the incidence of hepatocellular neoplasms. 1-Am-2-MeA increased the incidence of renal neoplasms and 2-Me-1-NA increased the incidence of sc fibromas in a dose-related manner. In mice, AA increased the incidence of hepatocellular carcinomas and 2-Me-1-NA increased the incidence of sc hemangiosarcomas. 1-Am-2-MeA did not appear to be carcinogenic in the mouse.

Nephrotoxicity was associated with the feeding of AA to female rats and 1-Am-2-MeA to mice. (11 refs)

- 79-6263 Potential Contamination from Feeding Test Chemicals in Carcinogen Bioassay Research: Evaluation of Single- and Double-Corridor Animal Housing Facilities. (Eng) Sansone, E. B. (Environmental Control and Res. Lab., NCI Frederick Cancer Res. Center, Frederick, MD 21701); Losikoff, A. M. *Toxicol Appl Pharmacol* 50(1): 115-121; 1979.

The magnitude and distribution of chemical contamination from single- and double-corridor animal rooms was determined by adding a tracer chemical, sodium fluorescein, to the granular diet of 200 Fischer F-344 male rats housed in single- and double-corridor rooms of equal size operated under identical protocols. The distribution of chemical contamination was monitored over a 7.5-day period. Differences between the two rooms were statistically indistinguishable ($\alpha = 0.05$) in all comparisons but two: the contamination of the room floors and of the worker's gloves; in both cases, the single-corridor room contamination was greater. The difference between the floor data was attributed to the traffic patterns required by the rooms' configuration; in the presence of confirming findings from any other articles of clothing or animal care and maintenance operations, the glove findings were discounted. Floor contamination outside the vestibule and clean corridor doors suggested that the relative cross-contamination potential of single- or double-corridor facilities was about 6 to 1. If more than one room opened off the vestibule, the ratio could be about 20 to 1. It is suggested that the potential for cross-contamination can be most effectively and most economically reduced by controlling contamination at the source. (5 refs)

- 79-6264 Mutagenic Activity of Rhodamine Dyes and Their Impurities as Detected by Mutation Induction in *Salmonella* and DNA Damage in Chinese Hamster Ovary Cells. (Eng) Nestmann, E. R. (Mutagenesis Section, Environmental and Occupational Toxicology Div., Health Protection Branch, Dept. Natl. Health and Welfare, Ottawa, Ontario, K1A 0L2, Canada); Douglas, G. R.; Matula, T. I.; Grant, C. E.; Kowbel, D. J. *Cancer Res* 39(11): 4412-4417; 1979.

Commercial rhodamine dyes 6G and B were examined for induction of genetic effects using the *Salmonella*/mammalian microsome assay for mutation and Chinese hamster ovary (CHO) cells in vitro for detection of DNA strand breakage. Rhodamine B (0.25-4.0 mg/plate) was mutagenic in *Salmonella* strains TA1538 and TA98 (frameshift mutation) but not in strains TA1535, TA100 (both base substitution mutation) or TA1537 (frameshift mutation). Purified rhodamine B lost most of its mutagenicity while its impurities demonstrated the same extent of mutagenicity as the commercial dye. Rhodamine 6G (7.8-1,000 μ g/plate) was mutagenic in strains TA1538, TA98, TA1537, and TA100. It induced a doubling of revertants at only 3% (7.8 μ g) of the dose required for a doubling by rhodamine B (250 μ g) in strain TA1538. At its max, rhodamine 6G induced a 30-fold increase of revertants in strain TA1538, whereas the max increase induced by rhodamine B was 9-fold. Compared with the commercial dye, purified rhodamine 6G lost 22%-23% of its mutagenicity, but it still induced a 24-fold increase in revertants. Rhodamine 6G (9×10^{-5} M) and rhodamine B (9.6×10^{-4} M) caused damage in single strands of DNA in CHO cells as detected by alkaline sucrose sedimentation. Rhodamine 6G was more toxic than rhodamine B in both the bacterial and mammalian assays. Both dyes required activation by

Aroclor 1254-induced rat liver homogenate (S9) for induction of genetic activity. These results indicate that purified rhodamine 6G is potentially mutagenic while purified rhodamine B shows little mutagenicity. (22 refs)

- 79-6265 Mechanism of Enhancement of Polynucleotide Binding to Cells by Mutagens. (Eng) Noronha-Blob, L. (Lab. Cellular and Molecular Biology, Gerontology Res. Center, Natl. Inst. Aging, Baltimore, MD 21224); Pitha, J. *Biochemistry* 18(15): 3206-3209; 1979.

The mechanism of the enhanced binding of polyuridylyl[poly(U)] to WI-38 human fibroblasts was studied in the presence of compounds known to bind DNA. Fibroblast monolayers exposed to 10 ml of a soln containing 61 μ g/ml poly(U) bound approx 0.2 picogram/cell of polynucleotide, and saturation occurred within a few minutes. When cells were exposed to both poly(U) and proflavine (PF:100 μ g/ml), poly(U) binding was increased 10- to 20-fold. The increase was both time- and PF concentration-dependent. The PF-mediated enhancement was completely abolished by a 10-min wash with saline, and MgCl₂ and NaCl were equally effective. Thus, the PF-augmented binding of poly(U) to the cell surface appeared to be ionic. Enhanced polynucleotide binding was observed only upon simultaneous, not sequential, exposure to poly(U) and PF. The binding of the basic macromolecule diethylaminoethyl-dextran was only slightly enhanced by PF. The binding of poly(U) was not enhanced by ethylenediamine, primaquine, or quinacrine, but it was enhanced by acridine orange, and 9-aminoacridine, and Hoechst 33258; 9-aminoacridine was less effective in this respect than PF. When PF or Hoechst 33258 was attached by firm chemical bonds to the soluble polysaccharide dextran, their ability to enhance the binding of poly(U) to fibroblasts was lost. A model for the enhanced binding of poly(U) is proposed, based on the cooperative formation of stacked complexes of cationic dye located between the cell surface and the bound poly(U). (18 refs)

- 79-6266 Tritiated Thymidine as a Broad Spectrum Initiator in Transplacental Two-Stage Carcinogenesis, with Phorbol as Promoter. (Eng) Armuth, V. (Experimental Biology Unit, Weizmann Inst. Science, Rehovoth, Israel); Berenblum, I. *Int J Cancer* 24(3): 355-358; 1979.

To determine whether [³H]thymidine (HTdR) acts as an initiator in transplacental two-stage carcinogenesis, pregnant BALB/c mice received a single sc injection of 200 μ Ci HTdR on day 15 of gestation. Starting 10 days after birth, the offspring received phorbol (0.25 μ mole 2x/wk x 3, then 0.50 μ mole 2x/wk x 22, ip) for 25 wk and were examined for tumor induction for 18 mo. There was a significant increase in the total tumor incidence (12/27) in the phorbol-treated male offspring of the HTdR-injected mothers compared with controls (1/25, $p < 0.001$). The main constituents of this increase were lung adenomas (7/27) and liver tumors (5/27), but taken separately the increase in incidence of these two types was only of borderline significance. Hepatic tumors were detected in phorbol-treated female offspring but not in their untreated counterparts. The incidences of other kinds of tumors in male and female phorbol-treated offspring were not significantly increased. The direct carcinogenicity of HTdR, both in the mothers and in the offspring, was relatively low or even nonexistent. The results suggest that HTdR could be used as a broad spectrum initiator for transplacental two-stage carcinogenicity studies to determine the organ specificity of different promoting agents. (18 refs)

- 79-6267 Rapid Release of Fibronectin from Human Lung Fibroblasts by Biologically Active Phorbol Esters. (Eng) Keski-Oja, J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20205); Shoyab, M.; De Larco, J. E.; Todaro, G. J. *Int J Cancer* 24(2): 218-224; 1979.

The ability of several biologically active phorbol esters to release fibronectin from cultured human lung fibroblasts into medium was determined by a sensitive radioimmunoassay technique. The esters released fibronectin from the cells into the medium within 2 hr, producing concomitant changes in cellular morphology. The quantity of fibronectin released was dose-, time- and promoter-dependent. The earliest release of fibronectin occurred within 30 min of onset of incubation. Alterations in membrane topology elicited by the phorbol esters appear to be responsible for the rapid release of fibronectin molecules. (38 refs)

- 79-6268 Effect of Phorbol Ester Tumor Promoters on the Expression of Melanogenesis in B-16 Melanoma Cells. (Eng) Mufson, R. A. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032); Fisher, P. B.; Weinstein, I. B. *Cancer Res* 39(10): 3915-3919; 1979.

The effects of phorbol esters on the growth and differentiation of the C3 clone of B16 melanoma cells were studied. B16 cells attained a low basal melanin content 24 hr after plating, then began synthesizing large amounts of pigment upon reaching confluence on day 5. In cultures treated with 8×10^{-8} M 12-O-tetradecanoylphorbol-13-acetate (TPA) 24 hr after plating, the increased synthesis of pigment was delayed for 48 hr. This lag was not due to an effect of TPA on the cellular growth rate or the time at which the cultures reached confluence, and there was no inhibitory effect on cellular cloning efficiency. The escape from TPA-mediated inhibition, which occurred after about 48 hr, was not prevented by the addition of fresh TPA to the medium. Phorbol-12,13-didecanoate (PDD) and mezerein also caused a marked inhibition of melanin synthesis, although escape from inhibition by mezerein, the weaker tumor promoter, was more rapid than that from TPA-mediated inhibition. 4 α -phorbol-12,13-didecanoate, which is not a tumor promoter on mouse skin, did not inhibit melanogenesis. B16 cells were most sensitive to TPA-induced inhibition of melanin synthesis when cells were plated in TPA-containing medium or when the compound was added during the first 24 hr after plating. Melanin synthesis induced by melanin stimulating hormone (MSH) was blocked by TPA added 24 hr in advance of or, to a lesser extent, at the same time as MSH. The TPA sensitivity of the B16 stock cultures declined somewhat with the passage of time. (22 refs)

- 79-6269 The Effect of Phorbol Myristate Acetate on Human Lymphocytes. An Ultrastructural Study. (Eng) Skinner, L. F. (Dept. Pathology, Univ. Saskatchewan, Saskatoon S7N 0W0, Canada). *Exp Mol Pathol* 31(1): 36-43; 1979.

The ability of phorbol myristate acetate (PMA) to agglutinate normal human lymphocytes was compared with that of phytohemagglutinin (PHA), and the ultrastructural changes induced by PMA were studied. Lymphocyte agglutination was first noted microscopically at 1 hr, and by 24 hr agglutinates were evident macroscopically. The ultrastructural findings in the PMA-stimulated lymphocytes after 48 and 72 hr indicated blast transformation of the nucleus, increases in cytoplasm and ribosomes, and occasional "annulate lamellae." Apart from the annulate

lamellae, the changes were generally similar to those observed in PHA-stimulated lymphocytes. The data suggest that the initial action of PMA is on the cell membrane. (11 refs)

- 79-6270 Interaction of the Tumor Promoter 12-O-Tetradecanoylphorbol-13-Acetate with Cells in Mixed-Lymphocyte Culture. (Eng) Mastro, A. M. (Dept. Biochemistry and Biophysics, Pennsylvania State Univ., University Park, PA 16802); Krupa, T. A.; Smith, P. *Cancer Res* 39(10): 4078-4082; 1979.

The effects of 12-O-tetradecanoylphorbol-13-acetate (TPA) on bovine lymphocytes in mixed-lymphocyte reactions (MLR) were studied. Preincubation of cells with TPA for several days prevented them from synthesizing DNA in the MLR and also inhibited blastogenesis. A further 3-day incubation in fresh medium before mixing restored the ability of the cells to undergo the MLR. Although pretreatment of either responding or stimulating cells inhibited DNA synthesis in the MLR, responding cells were most sensitive to TPA treatment. Increasing the ratio of untreated stimulating cells to TPA-treated responders did not overcome the inhibitory effect of TPA on the responders, but the effect of the TPA-treated stimulating cells depended on cell dose. The response of TPA treatment showed some variability from animal to animal. The data are consistent with the idea that TPA acts by changing the cell surface recognition structures and/or indirectly, through activation of a subpopulation of cells, by blocking the proliferative response. (36 refs)

- 79-6271 Differential Response of Myofibrils and 10-nm Filaments to a Cocarcinogen. (Eng) Toyama, Y. (Dept. Anatomy, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19104); West, C. M.; Holtzer, H. *Am J Anat* 156(1): 131-137; 1979.

Multinucleated myotubes containing large numbers of striated myofibrils and longitudinally-oriented 10-nanometer (nm) filaments were treated with the cocarcinogen phorbol-12-myristate-13-acetate (PMA) for 24, 48 or 72 hr. The inhibitory effect of PMA on the accumulation of myofibrils was evident within 24 hr, and by 72 hr virtually all striated myofibrils had disappeared. In contrast, the density of the 10-nm filaments was greatly enhanced in these myofibril-depleted myotubes. These effects were not due to a generalized cytotoxicity, as PMA stimulated the replication of the presumptive myoblasts and fibroblasts present in these cultures. The myotubes assembled a new set of striated myofibrils 24 hr after removal of PMA, and the density of 10-nm filaments diminished proportionately. (12 refs)

- 79-6272 Effects of Phorbol Ester Tumor Promoters in Platelet Aggregation and Platelet Production of Cyclooxygenase Products. (Eng) Mufson, R. A. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032); Kulkarni, P.; Eakins, K. E.; Weinstein, I. B. *Cancer Res* 39(9): 3602-3606; 1979.

An attempt was made to correlate the structure-activity relationships previously established for the tumor-promoting activity of phorbol esters with their platelet-aggregating activity. The tumor promoters 12-O-tetradecanoylphorbol-13-acetate (TPA),

phorbol-12,13-didecanoate, and mezerein, in the range of 10^{-8} M, caused aggregation of washed rabbit platelets. The lag time between the addition of tumor promoters and the onset of aggregation was inversely proportional to the concentration of the compounds. 4 α -Phorbol-12,13-didecanoate, which is inactive as a tumor promoter, did not induce platelet aggregation, and 4-O-methyl-12-O-tetradecanoylphorbol-13-acetate, which is a weak tumor promoter, had low activity in this assay. Arachidonic acid also caused platelet aggregation. Arachidonic acid-induced aggregation was rapid, reversible, and accompanied by the production of thromboxane A_2 -like activity, as determined by bioassay on rabbit aorta and celiac artery strips. This aggregation was blocked by the cyclooxygenase inhibitor indomethacin. TPA-induced aggregation, however, was slow and irreversible. It was not accompanied by production of thromboxane A_2 -like activity and was not blocked by indomethacin. TPA-induced aggregation was accompanied by the enhanced production of a vasoactive material that contracted only rabbit celiac artery and, in contrast to thromboxane A_2 , was stable for 10 min at 37 C. This material was not ADP or 5-hydroxytryptamine. The results indicate that the structural requirements of diterpenes for tumor promotion are similar to those for platelet-aggregating activity. The generation of prostaglandin synthetase (cyclooxygenase) products does not appear to be required for phorbol ester-induced aggregation. The latter is accompanied by the production of an unidentified vasoactive material that may be related to the mechanism of aggregation. (20 refs)

- 79-6273 The Effect of a Tumor Promoter, 12-O-Tetradecanoyl-phorbol-13-acetate (TPA), on Sister-Chromatid Exchange Formation in Cultured Chinese Hamster Cells. (Eng) Loveday, K. S. (Genetics Div., Mental Retardation Center, Children's Hosp. Medical Center, Boston, MA 02115); Latt, S. A. *Mutat Res* 67(4): 343-348; 1979.

At 0.3-3.0 μ g/ml, the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) did not increase the sister-chromatid exchange (SCE) frequency in either Chinese hamster ovary (CHO) or lung (V79) cells cultured in the presence of 2×10^{-5} or 1×10^{-4} M 5-bromodeoxyuridine. Moreover, TPA did not alter the induction of SCE's in CHO cells by mitomycin C (0.03 μ g/ml) during the first three cycles following the addition of the alkylating agent. These SCE induction data do not support the hypothesis that tumor promotion by TPA depends on the enhancement of mitotic recombination. (25 refs)

- 79-6274 Prostaglandin E and F Levels in Mouse Epidermis are Increased by Tumor-promoting Phorbol Esters. (Eng) Ashendel, C. L. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Boultwell, R. K. *Biochem Biophys Res Commun* 90(2): 623-627; 1979.

Prostaglandins E (PGE) and F (PGF) levels were determined by radioimmunoassay in female CD-1 mouse epidermis after topical application of phorbol esters. Peak PGE levels (six times basal levels) were detected at 6 and 24 hr after treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA; 17 nanomoles). PGF levels also peaked twice, increasing threefold at 9 hr and tenfold by 72 hr after TPA treatment. The phorbol effect on PG levels lasted for 5-7 days. The increase in PGE levels was dose dependent. The activities of various phorbols for increasing PGE and PGF levels were TPA > phorbol-12,13-didecanoate > phorbol-12,13-dibenzoate > phorbol-12,13-diacetate \approx phorbol. Various doses of

the nonsteroidal anti-inflammatory drugs indomethacin, flufenamic acid, and naproxen were applied topically to mice 2 hr prior to treatment with 17 nanomoles of TPA and epidermal PGE levels were measured 6 hr after TPA. The doses of indomethacin, flufenamic acid, and naproxen that inhibited the TPA-increased PGE levels by 50% were 46, 110, and 135 nanomoles, respectively. For the five phorbol compounds tested, the increased epidermal PG levels paralleled ornithine decarboxylase induction and increased DNA synthesis and skin papilloma formation in initiated mice. These results support the hypothesis that PGs are involved in the mechanism of action of tumor-promoting phorbol esters. (19 refs)

- 79-6275 Ornithine Decarboxylase Activity, Cell Proliferation, and Tumor Promotion in Mouse Epidermis In Vivo. (Eng) Marks, F. (German Cancer Res. Center, Inst. Biochemistry, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Bertsch, S.; Furstenberger, G. *Cancer Res* 39(10): 4183-4188; 1979.

The effect of different phorbol esters and of mechanical treatment on the activity of ornithine decarboxylase in mouse epidermis was investigated in vivo. The strong tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), as well as the weak promoters phorbol dibenzoate and the TPA analog 12-O-tetradeca-2-cis,4-trans-6,8-tetradecanoylphorbol-13-acetate strongly increased the activity of the enzyme and the intraepidermal level of putrescine, with a max at 5 hr after application, when applied in doses that evoke comparable proliferative and irritant responses in skin. The 4-O-methyl ether of TPA did not show such effects. Mechanical removal of the uppermost horny layer led to an increase in ornithine decarboxylase activity after 4-8 hr, while skin massage showed only a minute effect under conditions in which both treatments exhibit about the same mitogenic efficiency. Rubbing did not promote tumor development in this study, and the same has been previously found to be true for massage. After skin massage, ornithine decarboxylase induction was unaffected by treatments that alter the cyclic AMP level in epidermis (inhibition of phosphodiesterase, β -adrenergic stimulation, and injection of dibutyl cyclic AMP) or by the injection of epidermal G chalone. The results indicate that no clear-cut correlation exists between epithelial cell proliferation, development of hyperplasia, and tumor promotion on the one hand and activation of epidermal ornithine decarboxylase on the other. (26 refs)

- 79-6276 Dynamics of Neoplastic Development in Carcinogen-exposed Tracheal Mucosa. (Eng) Terzaghi, M. (Biology Div., Oak Ridge Natl. Lab., PO Box Y, Oak Ridge, TN 37830); Nettesheim, P. *Cancer Res* 39(10): 4003-4010; 1979.

An in vitro assay of the formation of epithelial foci (EF) was used to study cellular changes occurring in the tracheal epithelium of specific-pathogen-free female Fischer 344 rats exposed over a 4-wk period to wax pellets containing 12-O-tetradecanoylphorbol-13-acetate (TPA, 100 μ g) or dimethylbenz(a)anthracene (DMBA, 165 μ g). Cell suspensions from each trachea were seeded into culture dishes, and the number of EF was scored 1 mo later. No EF were seen in cultures of normal tracheal cells or those exposed to TPA. In 80%-90% of cultures from tracheas exposed to DMBA up to 4 mo previously, 3-4 EF were found per culture, and in those from tracheas exposed to DMBA 4-8 mo previously, the number of EF per culture increased three- to fivefold. During the 80 mo after DMBA exposure, EF that could be subcultured increased from

53% to 84%, and EF that could be subcultured and grown in soft agar increased from 23% to 57%. The frequency of EF that could not be subcultured dropped from 47% to 16%, and the relative frequency of EF that could be subcultured but would not grow in soft agar remained constant. The data are consistent with a gradual conversion of epithelial focus-forming units (EFFUs) with limited growth capacity to EFFUs with neoplastic growth capacity as a function of time after carcinogen exposure. At 8 mo, 80% of DMBA-exposed tracheas contained cells with neoplastic potential, suggesting that, if left in the host animals, only a fraction of these cells would actually succeed in establishing malignant tumors. (29 refs)

79-6277 Effects of Phorbol Ester Tumor Promoters on Arachidonic Acid Metabolism in Chick Embryo Fibroblasts. (Eng) Mufson, R. A. (Div. Environmental Sciences and Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, 701 W. 168 St., New York, NY 10032); DeFeo, D.; Weinstein, I. B. *Mol Pharmacol* 16(2): 569-578; 1979.

The phorbol ester tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA: 10^{-7} - 10^{-9} M) caused a rapid (1-3 hr after addition) release of arachidonic acid and prostaglandins E₂ and F_{2 α} from chick embryo fibroblasts. This effect was inhibited by cycloheximide and puromycin. Prostaglandin release was more sensitive to inhibition than was arachidonic acid release. Indomethacin, a cyclooxygenase inhibitor, completely blocked TPA-induced prostaglandin synthesis and slightly enhanced arachidonic acid release. Despite the complete suppression of prostaglandin synthesis, indomethacin caused only a 20-30% inhibition of TPA induction of plasminogen activator. Phorbol-12,13-didecanoate, phorbol-12,13-dibenzoate and mezerein were also potent inducers of arachidonic acid and prostaglandin release, while phorbol and 4 α -phorbol didecanoate were inactive. All-*trans*-retinoic acid (10^{-5} - 10^{-6} M) inhibited TPA-induced arachidonic acid and prostaglandin release; retinyl palmitate and β -carotene were less effective inhibitors. The effects of the phorbol compounds and retinoids on arachidonic acid release in this cell culture system correlate with their known effects on tumor promotion in mouse skin. Deacylation of membrane phospholipids may, therefore, be an important contributing factor in the action of this class of tumor promoters. (28 refs)

79-6278 Phorbol Ester Induced Prostaglandin Synthesis and [³H]-TPA Metabolism by TPA-sensitive and TPA-resistant Friend Erythroleukemia Cells. (Eng) Yamasaki, H. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Mufson, R. A.; Weinstein, I. B. *Biochem Biophys Res Commun* 89(3): 1018-1025; 1979.

The effect of the potent mouse skin tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) on the release of [³H]arachidonic acid and [³H]prostaglandin synthesis in TPA-resistant and TPA-sensitive clones of Friend erythroleukemia cells (FELC) is reported, along with the metabolism of [³H]TPA in these clones. TPA caused the release of arachidonic acid and prostaglandins E₂ and F_{2 α} from FELC. This effect was not seen with a subclone that is resistant to both TPA-induced inhibition of differentiation and TPA-induced adhesion. TPA-sensitive and TPA-resistant clones metabolized [³H]TPA and phorbol-13-monoacetate [P(13)A] at the same rate. P(13)A had no effect on the differentiation or adhesion of FELC. Together with previous

findings, these results suggest that TPA-induced changes in membrane lipid metabolism are closely linked to the effects of TPA on growth, differentiation, and adhesion. The resistance of a subclone of FELC to TPA appears to be at the level of membrane action rather than the metabolism of TPA. (21 refs)

79-6279 Effects of Dietary Fat on Hepatic Mixed-Function Oxidases and Hepatocellular Carcinoma Induced by Aflatoxin B₁ in Rats. (Eng) Newberne, P. M. (Room E18-613, Massachusetts Inst. Technology, Cambridge, MA 02139); Weigert, J.; Kula, N. *Cancer Res* 39(10): 3986-3991; 1979.

The effects of dietary beef fat (13% or 28% of diet) and corn oil (2%, 15%, or 30%) on the induction of hepatocarcinomas in male Sprague-Dawley rats that received intragastric doses of aflatoxin B₁ (AFB: 7 mg/kg as a single dose or 25 μ g/day for 5 or 15 days) were studied. Rats fed beef fat had increased liver fat concentrations (4.61% and 4.24% of body wt in 28% and 13% beef fat groups, respectively) and increased mortality due to acute AFB toxicity (63.3% and 83.8% in 28% and 13% groups, respectively) than did those given corn oil. The resting microsomal enzyme activity levels increased sequentially in all rats over a 3-wk period, the increases in many cases being significantly higher ($p \leq 0.05$) in the rats given corn oil than in those given beef fat. In rats exposed to AFB, corn oil also significantly enhanced the induction of enzyme activity by AFB, compared with induction in those given beef fat. Hepatic tumor incidence was higher in rats fed the high-corn oil diet during and after AFB exposure (100%) and in those fed the high corn oil diet after AFB exposure (66%) than in those fed beef fat, whether or not the diets were fed during AFB exposure (51%-53%, $p = 0.02$). The data suggest that corn oil may act as a tumor promoter through microsomal enzyme induction and AFB activation. (45 refs)

79-6280 Biochemical Studies During Aflatoxin B₁-induced Liver Damage in Rats Fed Different Levels of Dietary Protein. (Eng) Mirmomeni, M. H. (Biochemistry Dept., Univ. Kermanshah, Kermanshah, Iran); Suzangar, M.; Wise, A.; Messripour, M.; Emami, H. *Int J Cancer* 24(4): 471-476; 1979.

The biochemical aspects of liver damage induced by aflatoxin B₁ (AFB: 2 mg/kg in the diet) in male Sprague-Dawley rats fed high (HP)- or low (LP)-protein diets were studied. AFB enhanced and subsequently inhibited the growth of rats fed the HP diet but had no effect on the growth of those given the LP diet. In rats fed the HP diet, AFB increased lactic dehydrogenase (LDH) levels by 82% and 210% at 16 and 24 wk, respectively, over the levels in HP-fed rats not receiving AFB. At 24 wk, the HP-AFB-fed rats showed increases of 114%, 45%, and 76% in alkaline phosphatase (AP), SGOT, and SGPT levels, respectively, over the levels in HP-fed rats not given AFB. SGPT was increased 59% over control (LP diet without AFB) at 24 wk in the rats given the LP diet with AFB. Aflatoxin M₁ (AFM) and aflatoxin P₁ (AFP) excretion tended to be lower in the HP than in the LP rats. AFB feeding increased kidney wt, but not liver wt, in relation to body wt, especially in HP-fed rats. The dietary protein level did not significantly affect the appearance of the liver, but AFB caused degeneration and necrosis in LP- and HP-fed rats and the development of hyperplastic nodules in HP-fed rats. It is concluded that LDH, AP, and the ratio of urinary excretion of AFM to AFP could be useful tests for the diagnosis of AFB-induced precancerous liver changes in humans. (no refs)

- 79-6281 Aflatoxigenic Potential of Dried Figs, Apricots, Pineapples, and Raisins. (Eng) Morton, S. G. (Dept. Biology, Virginia Commonwealth Univ., Richmond, VA 23284); Eadie, T.; Llewellyn, G. C. *J Assoc Off Anal Chem* 62(4): 958-962; 1979.

Dried figs, apricots, raisins, and pineapples were evaluated with respect to their potential for contamination by aflatoxins. Spores from three aflatoxigenic strains were applied to the surfaces of the dried fruits, half of which had been autoclaved prior to inoculation. Mold growth was monitored daily for 45 days, after which the aflatoxin present was extracted and analyzed. No mold growth or sporulation of aflatoxin was found on any of the 18 raisin samples, whereas extensive mold growth was observed on all pineapple slices, the amount of aflatoxin depending on fungus strain. None of the cooked figs showed mold growth or sporulation, whereas all uncooked figs did. None of the figs produced any aflatoxin B₂. All of the cooked apricots produced some aflatoxin, the amounts of B₁ and G₁ being generally equal. The one set of uncooked apricots that produced aflatoxins produced only small amounts of G₁ and even lesser amounts of B₁. The overall potential for toxin production in the dried fruit was apricot > fig > pineapple > raisin. Among the cooked substrates, the order was apricot > pineapple > fig > raisin. For raw dried fruit, the ranking was fig > pineapple > apricot > raisin. (22 refs)

- 79-6282 Metabolic Activation of Polycyclic Aromatic Carcinogens: A Theoretical Study. (Eng) Umans, R. S. (Dept. Chemistry, Wellesley Coll., Wellesley, MA 02181); Koruda, M.; Sardella, D. J. *Mol Pharmacol* 16(2): 633-642; 1979.

Huckel molecular orbital calculations were performed on a series of polycyclic aromatic hydrocarbons (PAH) to obtain bond localization energies and π -electron stabilization energies for the reaction sequence through which the "bay region" diol epoxide is formed. These calculations suggest that carcinogenic PAH and noncarcinogenic PAH may exhibit different behavior at three points in the sequence. The highest localization energies for formation of the initial epoxide are exhibited exclusively by a block of noncarcinogenic PAH, suggesting that they may form only minimal amounts of the initial dihydrodiol. Of the remaining PAH, the carcinogens generally exhibit greater π -electron stabilization than do noncarcinogens following opening of both the initial epoxide and the diol epoxide rings, possibly indicating more facile production of the initial dihydrodiol and of the final biomolecule adduct. The relative potencies of the 12 carcinogenic PAH considered, as measured by the Iball Index, can be satisfactorily reproduced (correlation coefficient = 0.90) through an equation combining indices for formation of the initial epoxide and for π -electron stabilization of its ring-opened cation. (32 refs)

- 79-6283 Relationships Between Carcinogenicity and Theoretical Reactivity Indices in Polycyclic Aromatic Hydrocarbons (Letter to Editor). (Eng) Osborne, M. R. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Buckinghamshire HP8 4SP, England). *Cancer Res* 39(11): 4760-4761; 1979.

An earlier paper proposed that the parameter Q_b , which represents the positive charge at the bay-region position for various hydrocarbons, was negatively correlated with the carcinogenicity of the compound. However, the use of Q_b gave rise to a number of false positives, ie, compounds which have a low Q_b value but are not

carcinogenic. These anomalies derive from the fact that in the presumed diol-epoxide carbonium ions from these hydrocarbons, the positive charge resides largely at two or three positions instead of being delocalized all around the aromatic nucleus. In response to this paper, it is proposed instead that the ease of carbonium ion formation is best estimated by the uniformity of distribution around the molecule as a whole. A parameter which expresses this uniform distribution of charge is σ/a_o , the sum of the nonbonding molecular orbital coefficients. This quantity is as easy to calculate as is Q_b . It varies from 1.0 for a localized positive charge to a little more than 3 for ions derived from the highly delocalized tribenzo(a)pyrenes. The carcinogenic potencies of 39 hydrocarbons were plotted against σ/a_o for the most reactive diol-epoxides they would be expected to form. There was a good correlation between carcinogenicity and σ/a_o , and the anomalies encountered with Q_b were largely removed. The criterion $\sigma/a_o > 2.6$ appears to distinguish carcinogens from noncarcinogens with few exceptions. (6 refs)

- 79-6284 Cigarette Smoke Inhalation Studies in Inbred Syrian Golden Hamsters. (Eng) Bernfeld, P. (Bio-Res. Consultants, 9 Commercial Ave., Cambridge, MA 02141); Homburger, F.; Soto, E.; Pai, K. J. *J Natl Cancer Inst* 63(3): 675-689; 1979.

Inbred Syrian golden hamsters from strain B10 15.16, which is susceptible to laryngeal carcinogenesis by cigarette smoke inhalation, were exposed to smoke from four types of cigarettes at two dose levels. Fifty-seven hamsters were exposed to smoke from an all-tobacco cigarette during two 12-min periods (actual smoke exposure 27 sec out of each minute) for ≥ 59 wk at a smoke concentration of 22%; 47.4% developed laryngeal cancer, and in 36.8% of the exposed animals, the cancer was invasive. At a smoke concentration of 11%, 6.8% of exposed hamsters developed invasive carcinoma. Smoke from cigarettes containing only Cyrel (a tobacco supplement) induced no carcinomas. Replacement of part of the tobacco by Cyrel resulted in a reduction of tumor induction proportionate to the amount of Cyrel in the cigarette. Tar deposition in lungs and larynxes was determined by means of a marker, decachlorobiphenyl, added to the cigarettes. Admixture of Cyrel to cigarettes reduced tar deposition in the respiratory tract. However, the amounts of tar deposited in the larynx when 100% Cyrel was smoked were still significant, even though no carcinomas were observed. Other dose-related changes observed in the smoke-exposed hamsters were laryngeal papillomas, laryngeal epithelial hyperplasia, tracheal epithelial hyperplasia, and metaplasia and accumulation of alveolar macrophages. It is concluded that smoke inhalation studies in unprimed, nose-breathing animals are unlikely to yield lung cancer, although such studies do cause laryngeal cancer under rigorous conditions such as those used in this study. (15 refs)

- 79-6285 Tumors and Hyperplastic Lesions in Syrian Hamsters Following Transplacental and Neonatal Treatment with Cigarette Smoke Condensate. (Eng) Nicolov, I. G. (Lab. Chemical Carcinogenesis, Inst. Oncology, Medical Acad., Sofia 1156, Bulgaria); Chernozemsky, I. N. *J Cancer Res Clin Oncol* 94(3): 249-256; 1979.

Cigarette smoke condensate (CSC) was tested for both transplacental carcinogenicity and carcinogenicity in neonates. CSC in olive oil was injected into adult outbred Syrian hamsters on the 10th-14th day of gestation (total dose 1.5-2.5 mg/g, ip) and

also in 12- to 14-day-old animals (total dose 0.5-1.5 mg/animal, sc). Following 15-25 mo of observation, benign and malignant neoplasms were found in 2/58 animals treated during pregnancy, in 17/51 transplacentally exposed offspring; and in 5/53 neonatally treated hamsters. In the last two groups, females developed neoplasms more frequently than males (46.2% vs 20% in offspring; 17.4% vs 3.3% in animals treated as neonates). Tumors were most frequently encountered in the adrenal glands, pancreas, female sex organs, and liver. Polycystic liver disease occurred in 86% of animals exposed to CSC transplacentally, 79% of those treated as neonates, and 28% of those serving as controls. No tumors were encountered in controls. The results indicate that CSC produces tumors in transplacentally and neonatally exposed hamsters, particularly females. (22 refs)

- 79-6286 Testing of Some Permitted Food Colours for the Induction of Gene Conversion in Diploid Yeast. (Eng) Sankaranarayanan, N. (Div. Radiological Protection, Bhabha Atomic Res. Center, Trombay, Bombay 400085, India); Murthy, M. S. *Mutat Res* 67(4): 309-314; 1979.

Twelve food colors used in India and elsewhere were tested for their ability to induce mitotic gene conversion in the diploid yeast, *Saccharomyces cerevisiae*. None of these substances induced mitotic gene conversion in yeast treated in either stationary-phase or log-phase culture. There was also no significant cell killing or inhibition of cell division, and the absence of such effects was not due to a lack of penetration of the dye into the cells. The results do not agree with the results of some genotoxicity tests conducted with microorganisms and mammalian cell systems, indicating the need for further testing. (18 refs)

- 79-6287 Photocarcinogenesis by Methoxypsoralen, Neutral Red and Proflavine. (Eng) Santamaria, L. (Istituto di Patologia Generale "C. Golgi", Centro Profilassi Prevenzione Diagnosi e Cura dei Tumori, Univ. Pavia, Pavia, Italy); Arnabaldi, A.; Daffara, P.; Bianchi, A. *Boll Chim Farm* 118(7): 356-362; 1979.

The potential tumorigenic effects of 8-methoxypsoralen (8-MOP: 5 µg), neutral red (NR: 100 µg), and proflavine (PF: 50 µg) all given topically 2x/wk in combination with fractionated exposure to long UV (UVA) or visible light (NR and PF) were studied in female Swiss albino mice. The mice were exposed to UVA or visible light 60 min for 15, 30, 45 or 60 min. All groups showed erythema phototoxicity 10-12 hr after irradiation. Tumors developed in all groups and included mammary adenocarcinomas (with lung metastases), mixed carcinosarcomas, lymphomas (with liver metastases), and adenocarcinoma of the thyroid (NR group). No tumors were detected in the area painted with the drugs. Forty-three percent of animals treated with 8-MOP and UVA developed tumors by the 60th wk after initial treatment with onset beginning at the 25th wk. In those treated with NR and visible light, 20% developed tumors by the 50th wk with onset at the 39th wk. In those treated with PF and visible light, 25% had tumors at the 60th wk with onset at the 29th wk. None of the control groups showed tumor development except for the group treated with UVA alone; in this group, 5/40 mice developed carcinomas. It appears that UVA with 2.6% of fluence at 313 nm is a long-term carcinogenic agent. Although the results indicate that there is an oncogenic risk in photochemotherapy for the treatment of skin diseases and oral and genital forms of herpes simplex virus infection, it is emphasized that this treatment has been used for years without any evidence

of an increase in cancer incidence in treated patient groups. (34 refs)

- 79-6288 Use of Hamster Hepatocytes to Metabolize Carcinogens in an In Vitro Bioassay. (Eng) Pooley, J. A. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701); Raineri, R.; Pienta, R. J. *J Natl Cancer Inst* 63(2): 519-524; 1979.

To provide metabolic activation of carcinogens that may more closely resemble that occurring in vivo, intact functional Syrian golden hamster hepatocytes were used to supplement the metabolic capacity of a hamster embryo cell transformation system. Basal levels of aryl hydrocarbon hydroxylase (AHH) were 20-fold greater and epoxide hydrolase (EH) activity was >100-fold higher in hepatocytes than in embryo cells. Induction of AHH with benz(a)anthracene was 7-fold higher and induction with 3-methylcholanthrene was 20-fold higher in hepatocytes than in embryo cells. Lethal x-irradiation of the hepatocytes had little effect on basal or induced levels of AHH or EH. The N-hydroxylase and deacetylase activities in hamster hepatocytes were 450 and 1,000 times greater, respectively, than those previously determined for hamster embryo cells. Embryo cells were treated with diethylnitrosamine, 2-nitrofluorene, or 4-aminoazobenzene in the presence and absence of lethally irradiated hepatocytes. No transformation was observed when the target cells were treated with these chemicals alone. However, when the target cells were treated with the carcinogens in the presence of hamster hepatocytes, transformation was observed with all three compounds. Thus, hepatocytes appear to metabolize these carcinogens to a form that is either biologically active or able to be activated further by the hamster embryo cells. (22 refs)

- 79-6289 The Formation of Dihydrodiols by the Chemical or Enzymic Oxidation of 7-Hydroxymethyl-12-methylbenz(a)anthracene and the Possible Role of Hydroxymethyl Dihydrodiols in the Metabolic Activation of 7,12-Dimethylbenz(a)anthracene. (Eng) Macnicoll, A. D. (Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England); Burden, P. M.; Ribeiro, O.; Hewer, A.; Grover, P. L.; Sims, P. *Chem Biol Interact* 26(2): 121-132; 1979.

An attempt was made to identify the dihydrodiols formed from 7-hydroxymethyl-12-methylbenz(a)anthracene (HM-MBA) by rat liver microsomal fractions, mouse skin in short-term organ culture, and chemical oxidation in an ascorbic acid/ferrous sulfate/EDTA system by a combination of thin-layer chromatography and high-pressure liquid chromatography. The 3,4-, 8,9-, and 10,11-dihydrodiols were formed in all three systems. The 5,6-dihydrodiol was formed by the rat liver microsomal fractions and by chemical oxidation, but not by the mouse skin in short-term organ culture. The possible role of hydroxymethyl dihydrodiols in the in vivo metabolic activation of 7,12-dimethylbenz(a)anthracene (DMBA) in mouse skin was studied with the use of Sephadex LH-20 column chromatography. The results show that the hydrocarbon-nucleic acid products formed following the treatment of mouse skin in vivo with [³H]DMBA are not the same as those formed following the treatment of mouse skin under the same conditions with either 7-HM-MBA or 7-methyl-12-hydroxymethylbenz(a)anthracene. (20 refs)

- 79-6290 Photooxidation Products of 7,12-Dimethylbenz[a]anthracene. (Eng) Wood, J. L. (Dept. Biochemistry, Univ. Tennessee, Center Health Sciences, Memphis, TN 38163); Barker, C. L.; Grubbs, C. J. *Chem Biol Interact* 26(3): 339-347; 1979.

The main products of the photooxidation of 7,12-dimethylbenz[a]anthracene (DMBA) in aqueous solutions by photooxidation induced by laboratory lighting were characterized by high performance liquid chromatograms (HPLC), UV and mass spectrograms, and by comparisons with authentic samples in an effort to determine whether or not photooxidation could be a factor in studies of hydrocarbon metabolism and their interactions with tissue constituents. The products identified were the 7,12-epidioxy-7,12-dihydro-7,12-dimethyl-, 7,12-dione, 7-hydroxymethyl-12-methyl-, 12-hydroxymethyl-7-methyl-, 7-formyl-12-methyl-, 12-formyl-7-methyl-, and 12-hydroxy-12-methyl-7-one derivatives of benz[a]anthracene. The HPLC profile of products was similar to that obtained from oxidation of DMBA by "one-electron" reagents, singlet oxygen, or liver microsomal metabolism. The present results, taken together with those of other studies, suggest that the mechanism of photooxidation involves the generation of singlet oxygen by a photodynamic effect of DMBA. None of the products was found to be photosensitizing, however, and none was oxidized when dispersed in 10% methanol in water medium. Although it has been established that photooxidation could interfere with the results of hydrocarbon metabolism studies, a current literature review indicates that most investigators are taking this factor into account. (25 refs)

- 79-6291 Evidence for Translational Control of the Binding of 7,12-Dimethylbenz(a)anthracene to DNA of Murine Epidermal Cell in Culture. (Eng) Shoyab, M. (Meloy Labs., Inc., 6715 Electronic Drive, Springfield, VA 22151). *Chem Biol Interact* 25(2/3): 289-301; 1979.

The effects of various aryl hydrocarbon hydroxylase (AHH) inhibitors, antioxidants, inhibitors of DNA, RNA, and protein synthesis, and protease inhibitors on the binding of [7,12-³H]dimethylbenz[a]anthracene ([³H]DMBA) to DNA of murine epidermal cells in culture have been investigated. 7,8-Benzoflavone, 5,6-benzoflavone, and metyrapone (inhibitors of AHH) and the antioxidants butylated hydroxyanisole and butylated hydroxytoluene efficiently reduced the binding of [³H]DMBA to cellular DNA. Inhibitors of DNA and RNA synthesis did not affect this process, whereas inhibitors of protein synthesis (eg, cycloheximide) suppressed the binding of [³H]DMBA to cellular DNA. Protease inhibitors *p*-tosylamide-2-phenyl-chloromethyl ketone and *p*-tosyl-L-lysine chloromethyl ketone also reduced the interaction between DMBA and DNA. These results are consistent with previous findings that the binding of polycyclic aromatic hydrocarbons to cellular DNA depends on continuous protein synthesis but does not require DNA and RNA synthesis. Thus, the binding of DMBA to epidermal DNA appears to be regulated at the translational level; further regulation at the posttranslational level is also possible. (50 refs)

- 79-6292 Transformation of Feline Embryo Cells in Culture by a Chemical Carcinogen. (Eng) Rhim, J. S. (Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD 20205); Nelson-Rees, W. A.; Essex, M. *Int J Cancer* 24(3): 336-340; 1979.

A feline embryo cell line was treated in vitro with 0.1 or 0.01 µg/ml 7,12-dimethylbenz(a)anthracene (DMBA) for 7 days. Mor-

phological alterations, similar to those observed with feline sarcoma virus in feline embryo cells, were noted 45 days after DMBA treatment. However, this alteration was unstable and the cells reverted to normal-appearing epithelial-like cells after further subcultivation. The DMBA-treated cells formed colonies in soft agar, while the control cells treated with dimethylsulfoxide did not. One of these colonies was isolated and further treated with DMBA (0.01 µg/ml for 7 days), which resulted in stable morphological alterations. The DMBA-altered clone line had an increased growth rate, formed colonies in soft agar with high efficiency, and formed larger cell aggregates and grew in this aggregate form when suspended above an agar base. However, no progressively growing tumors were produced when cells were inoculated into nude athymic mice. The transformed lines were negative for feline oncornavirus-associated cell membrane antigen. The author concludes that the transition of a normal cell to a neoplastic one is reflected by a complex array of phenotypic changes and that the malignant and transformed phenotypes may be under separate genetic control or may represent a step-wise progression. (12 refs)

- 79-6293 The Association of Bacterial Mutagenicity of Hydrocarbon-derived 'Bay-Region' Dihydrodiols with the Iball Indices for Carcinogenicity and with the Extents of DNA-binding on Mouse Skin of the Parent Hydrocarbons. (Eng) Bartsch, H. (International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon, France); Malaveille, C.; Tierney, B.; Grover, P. L.; Sims, P. *Chem Biol Interact* 26(2): 185-196; 1979.

The mutagenicities of benz(a)anthracene, 7-methylbenz(a)-anthracene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, and benzo(a)pyrene together with those of their trans-dihydrodiols thought to be precursors of the biologically active bay-region vicinal diol epoxides, were examined in assays with *Salmonella typhimurium* TA100 using postmitochondrial supernatant fractions prepared from the livers of 3-methylcholanthrene-treated rats. The mutagenic activities were compared with: (1) the extents of reaction of the hydrocarbons (HC's) with mouse skin DNA, (2) the carcinogenicities of the HC's expressed as Iball indices, and (3) the activities of the HC's as tumor-initiating agents on mouse skin. Close positive associations were found between the microsome-mediated mutagenicities of the dihydrodiols that could yield bay-region diol epoxides and (1) the extents of reaction with DNA in HC-treated mouse skin and (2) the carcinogenic potencies of the parent HC's. Although these correlations are not perfect, the mutagenic activities of the HC's themselves in microsome-mediated assays with *S. typhimurium* show no correlation with their extents of DNA binding on mouse skin and a poor correlation with activities as initiating agents. These comparisons also indicated that there is a statistically significant positive correlation between carcinogenicity and the in vivo DNA binding on mouse skin treated with the HC's. There are differences in the metabolic pathways by which polycyclic HC's are activated in vivo and in vitro. (41 refs)

- 79-6294 Caffeine Inhibits the Binding of Dimethylbenz(a)anthracene to Murine Epidermal Cells DNA in Culture. (Eng) Shoyab, M. (Meloy Labs., Inc., 6715 Electronic Drive, Springfield, VA 22151). *Arch Biochem Biophys* 196(1): 307-310; 1979.

The effect of caffeine on the binding of dimethylbenz(a)anthracene (DMBA) to murine epidermal cell (MEC) DNA was studied in vitro. Caffeine suppressed the binding of DMBA to

MEC DNA while barely affecting the cell number or total DMBA associated with the cells. The degree of suppression was concentration-dependent, being 20% at 5 mM caffeine and approx 50% at 1 mM caffeine. Theophylline also inhibited the binding of DMBA to MEC DNA, although to a lesser extent than caffeine. Binding was not significantly affected by other chemical analogs of caffeine such as theobromine, xanthine, hypoxanthine, and uric acid. Dibutyryl cyclic AMP also did not significantly affect the binding of DMBA to MEC DNA, suggesting that caffeine and theophylline inhibited binding by a mechanism independent of cyclic AMP. The antitumorigenic effects of caffeine may be related to the ability of caffeine to inhibit the binding of active metabolites of carcinogens to the genetic material of cells. (32 refs)

- 79-6295 Polyadenylate-Polyuridyate Enhancement of 7,12-Dimethylbenzanthracene Skin Carcinogenesis. (Eng) Stenback, F. (Dept. Pathology, Univ. Kuopio, SF-70101 Kuopio, Finland); Curtis, G.; Ryan, W. *Experientia* 35(9): 1232-1233; 1979.

The effect of stimulation of the immune response by polyadenylate-polyuridyate (Poly AU) on 7,12-dimethylbenzanthracene (DMBA)-induced skin tumor formation was studied in female Swiss mice. The administration of Poly AU (100 µg/day, 5 days, ip) prior to topical DMBA application (100 µg) significantly increased skin tumor formation ($p < 0.02$), whereas the increase in skin tumor formation observed when Poly AU was administered after DMBA application was not significant. Most tumors were papillomas, and malignant tumors were seen only in animals receiving Poly AU after DMBA. The enhancement of tumor formation seen when the immune response was stimulated before carcinogen administration may be due to heightened carcinogen antibody formation. (14 refs)

- 79-6296 Aryl Hydrocarbon Hydroxylase in a Stable Human B-Lymphocyte Cell Line, RPMI-1788, Cultured in the Absence of Mitogens. (Eng) Freedman, H. J. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY 14263); Gurtoo, H. L.; Minowada, J.; Paigen, B.; Vaught, J. B. *Cancer Res* 39(11): 4605-4611; 1979.

Various parameters influencing aryl hydrocarbon hydroxylase (AHH) activity and inducibility were studied in a stable, immunologically defined human B-lymphocyte cell line (RPMI-1788) in long-term culture that shows high basal and inducible (AHH) activity in the absence of mitogenic prestimulation. This allowed attainment of enzyme levels and inducibility ratios comparable to those previously reported for fresh, mitogen-activated human lymphocytes. Dibenz(a,h)anthracene, at an optimal concentration of 0.3 µM and an optimal exposure time of 24 hr, was 30 times more potent an inducer than 1,2-benzanthracene. Maximal basal and induced enzyme activities and cell viability occurred at 48 hr of culture while the cell viability frequently declined by 72 hr of culture. Phytohemagglutinin M (200 µg/ml) and concanavalin A (40 µg/ml), which were not obligatory for AHH expression, enhanced AHH activity while, at the same time, decreasing the number of viable cells per culture. However, combinations of phytohemagglutinin and concanavalin A or those of either of these with pokeweed mitogen (itself ineffective) did not potentiate AHH activity over that obtained with phytohemagglutinin or concanavalin A used alone; however, various mitogen combinations were more cytotoxic than individual mitogens. Lipopolysaccharide

B did not affect either cell growth or AHH activity. Using cells cultured under optimal conditions and induced optimally with dibenz(a,h)anthracene, benzo(a)pyrene metabolites were analyzed by high-pressure liquid chromatography. The metabolite profile produced by these cells had several similarities with those produced by mitogen-stimulated, short-term-cultured human lymphocytes derived from fresh blood and by rodent liver microsomes. (54 refs)

- 79-6297 Transplantability of Chemically Induced Skin Tumors in Syngeneic Strains of Mice, Rats and Guinea Pigs. (Eng) Rasanen, O. (Dept. Pathology, Univ. Oulu, SF-90220 Oulu 22, Finland). *Exp Pathol (Jena)* 17(3): 121-127; 1979.

The transplantability of 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced skin tumors in syngeneic strains of mice (NMRI and hr/HR), rats (Sprague-Dawley), and guinea pigs was studied. Although DMBA was a relatively effective inducer of skin tumors, each group of treated animals yielded few tumors suitable for transplantation, since many of the tumors contained necrotic areas and inflammation. Tumors were grafted sc in 100 animals, and in 8 of these a tumor developed within 18 mo. One pleomorphic rat fibrosarcoma grew within 1 mo in all three grafted rats, the resulting tumors being histologically similar to the original. This tumor was injected with a myocardial suspension, which served as a supporting agent. The remaining five tumors grew in the host animals only after 10 mo or more, and it is not certain whether these tumors were really outgrowths of the grafts or spontaneous tumors. (26 refs)

- 79-6298 Immunologic Manipulation of DMBA Tumorigenesis in Hamster Cheek Pouch by DNCB Contact Hypersensitivity. (Eng) Mohammad, A. R. (Dept. Oral Pathology, Coll. Dentistry, Univ. Tennessee Center Health Sciences, Memphis, TN 38163). *J Oral Pathol* 8(3): 147-156; 1979.

The effects of dinitrochlorobenzene (DNCB) on experimental hamster cheek pouch tumors induced by topical dimethylbenzanthracene (DMBA) were studied in male Syrian golden hamsters. The cheek pouches were sensitized with DNCB before the initiation of DMBA tumorigenesis or by direct application to already developed tumors. Among animals treated with DNCB prior to the induction of tumorigenesis, there was an apparent delay in the onset of tumorigenesis and a decreased rate of tumor growth. Direct application of DNCB to established tumors seemed to temporarily arrest tumor growth, but the tumor growth rate later increased to approx that in untreated control hamsters. It is concluded that DNCB contact hypersensitivity may exert some influence on DNCB tumorigenesis. It appears that DNCB sensitization prior to tumor development is generally more effective than application of the allergen after tumor development. (16 refs)

- 79-6299 Apparent Rat Strain-related Sensitivity to Phorbol Promotion of Mammary Carcinogenesis. (Eng) Shellabarger, C. J. (Medical Dept., Brookhaven Natl. Lab., Upton, NY 11973); Holtzman, S.; Stone, J. P. *Cancer Res* 39(9): 3345-3348; 1979.

The promotion of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinogenesis by phorbol (4 mg twice weekly for 10 wk, ip) was studied in female Sprague-Dawley rats. In a previous

experiment. phorbol increased the incidence of mammary adenocarcinomas and lymphatic leukemia in female Wistar rats treated with DMBA. In the present experiment, phorbol given after DMBA (3 mg/100 g body wt by stomach tube) did not augment mammary adenocarcinoma or lymphatic leukemia incidence compared with the effects of DMBA alone. In the Sprague-Dawley rats, phorbol did not promote the incidence of mammary fibroadenomas in DMBA-treated rats, the incidence of mammary adenocarcinomas in procabazine-treated rats, or the incidence of mammary adenocarcinomas or fibroadenomas in x-irradiated rats. DMBA and procabazine, with or without phorbol, tended to induce more mammary tumors in the thoracic than in the abdominal mammary glands. X-irradiation tended to induce mammary neoplasms in approx equal numbers in the thoracic and abdominal glands. The results indicate that there is a strain-related difference in sensitivity between Wistar and Sprague-Dawley rats to phorbol promotion of DMBA carcinogenesis. (13 refs)

- 79-6300 Effects of Dietary Carbohydrate on the Incidence of Mammary Tumors Induced in Rats by 7,12-Dimethylbenz(a)anthracene. (Eng) Hoehn, S. K. (Dept. Biochemistry, Univ. Manitoba, Winnipeg, Manitoba R3E 0W3, Canada); Carroll, K. K. *Nutr Cancer* 1(3): 27-30; 1979.

The effects of purified diets containing sugars or starches on mammary tumor incidence in rats treated with 7,12-dimethylbenz(a)anthracene (DMBA) were compared. Groups of 20 female Sprague-Dawley rats were given a single po dose of 5 mg DMBA at 50 days of age, and 1 wk later they were transferred from a standard laboratory diet to purified diets containing 68% by wt of sugar (dextrose or sucrose) or starch (wheat, rice, or potato starch) and 5% by wt of fat. Sucrose and wheat starch were also fed at a level of 49% in a diet containing 20% fat. Rats fed the sugar diets developed significantly more mammary tumors than those fed the starch diets, at both low and high levels of dietary fat. These results are consistent with epidemiological data showing that age-adjusted breast cancer mortality in humans is positively correlated with sugar intake and negatively correlated with intake of complex carbohydrates. (18 refs)

- 79-6301 Incidence and Growth of Mammary Tumors Induced by 7,12-Dimethylbenz(a)anthracene as Related to the Dietary Content of Fat and Antioxidant. (Eng) King, M. M. (Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, Oklahoma City, OK 73104); Bailey, D. M.; Gibson, D. D.; Pitha, J. V.; McCay, P. B. *J Natl Cancer Inst* 63(3): 657-663; 1979.

To determine whether the ingestion of polyunsaturated fat decreases or antagonizes the inhibitory effect of antioxidants on 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumorigenesis, female Sprague-Dawley rats received one of three diets--high polyunsaturated fat, high saturated fat, and low fat--with and without butylated hydroxytoluene (BHT), beginning at 21 days of age; at 50 days of age, some animals in each group received a single dose of DMBA (10 mg, po) and were followed for development of mammary tumors. The av number of tumors induced per rat as well as tumor size was greatest in the group fed the unsaturated fat diet without BHT. The addition of BHT to the three diets decreased tumor incidence and tumor size in all groups. BHT completely eliminated the increased tumor incidence caused by high levels of saturated fat, but it was much less effective in reducing tumor incidence in animals fed the same level of polyunsaturated fat. The standard Ames mutagenicity assay was modified to determine the

capacity of liver microsomes to form mutagenic compounds from DMBA as a function of the diets fed, without prior treatment of the animals with Aroclor 1254 or phenobarbital. The effects of the various diets, either alone or with BHT, did not appear to be related to the capacity of liver microsomes to produce mutagenic compounds from DMBA, because no differences in the capacity of these microsomes to produce such compounds were observed in any of the dietary groups. (33 refs)

- 79-6302 Histo- and Biochemical Studies on Dehydrogenases in Tumorigenesis in Rat Zymbal Glands Induced with DMBA and DAS. (Eng) Morii, S. (Dept. Pathology, Kansai Medical Univ., Moriguchi, Osaka 570, Japan); Kumazawa, T.; Kusumoto, T.; Harada, H.; Tsubura, A.; Shikata, N. *Acta Histochem Cytochem* 12(4): 361-367; 1979.

The dehydrogenases of Zymbal glands containing tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA: 25 mg/kg, iv, at 51 and 66 days of age) plus 4-dimethylaminostilbene (0.004% of diet starting from age 57 days) were studied in male Wistar SLC rats. Within 11 wk, atypical hyperplasia of acinar cells was detected in the Zymbal glands. Micro- and macroscopically visible squamous cell carcinomas or sebaceous cell carcinomas were observed after 17 wk of treatment; some began to keratinize or became necrotic. Lactic dehydrogenase (LDH) activity was high in the atypical hyperplasias and moderate in the tumor tissues. Glucose-6-phosphate dehydrogenase and succinic dehydrogenase activities decreased during carcinogenesis and were absent from the keratinizing and necrotic areas. During tumorigenesis, malate dehydrogenase (MDH) activity dropped, so that the ratio of LDH/MDH was high in tumor-bearing rats. In general, this ratio began to increase at 8-10 wk and differed significantly ($p < 0.01$) from that in the untreated controls at 11 wk. (10 refs)

- 79-6303 Identification of the Proximate and Ultimate Forms of the Carcinogen 15,16-Dihydro-11-methylcyclopenta[a]phenanthren-17-one. (Eng) Coombs, M. M. (Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, WC2A 3PX, England); Kissonerghis, A. M.; Allen, J. A.; Vose, C. W. *Cancer Res* 39(10): 4160-4165; 1979.

Experiments were carried out to identify the metabolite responsible for the carcinogenicity of 15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one (I). Enzymatic hydrolysis of calf thymus DNA treated in vitro with I and a microsomal enzyme system followed by column chromatography disclosed two adduct fractions (A and B) eluting after the natural nucleosides. Isolation and hydrolysis of DNA from the skin of male Tyler's Original (TO) mice treated topically with I or from mouse embryo cells exposed to the carcinogen in culture gave mainly adduct B identical to that obtained in vitro. The seven main metabolites formed from I with the microsomal system were isolated by high-pressure liquid chromatography and individually incubated with DNA and the activating system; the DNA was subsequently recovered and analyzed. Adduct B arose from a single metabolite identified as a 3,4-dihydro-*trans*-3,4-dihydroxy derivative of I, on the basis of its UV and mass spectra together with its general chemical behavior. This metabolite was the most mutagenic metabolite in the Ames test and was more active than the carcinogen itself, indicating that it is the proximate form of the carcinogen. The UV spectrum of adduct B resembled that of a 1,2,3,4-tetrahydroderivative of I, but its chromatographic mobility on Sephadex LH-20 was markedly increased by inclusion of borate in the eluant, indicating a *cis*-diol

system. Since the 3,4-diol is *trans*, this suggests further metabolism of the benzo ring. It is therefore proposed that the ultimate carcinogen is a 1,2-dihydro-1,2-epoxy-3,4-dihydro-*trans*-3,4-diol of I. (37 refs)

- 79-6304 Mutagenicity and Tumorigenicity of Phenanthrene and Chrysene Epoxides and Diol Epoxides. (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NJ 07110); Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Mah, H. D.; Karle, J. M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 39(10): 4069-4077; 1979.

The biological activities of several epoxide and dihydro derivatives of chrysene and phenanthrene were evaluated via mutagenicity studies in *Salmonella typhimurium* strains TA98 and TA100 (ST) and Chinese hamster V79 cells (CHC) and skin tumorigenicity studies in female Charles River CD-1 mice. In ST, the bay-region (\pm)-1 β ,2 α -dihydroxy-3 α ,4 α -epoxy-7,8,9,10-tetrahydrochrysene (I) with the benzylic 1-hydroxy group *trans* to the bay-region epoxide oxygen (I) was four- to sixfold more mutagenic than its diastereomer, (\pm)-1 β ,2 α -dihydroxy-3 β ,4 β -epoxy-1,2,3,4-tetrahydrochrysene (II), and was over 40-fold more mutagenic than the K-region chrysene 5,6-oxide. In CHC, I was fourfold more mutagenic than II, and III was very weakly mutagenic. 3,4-Epoxy-1,2,3,4-tetrahydrochrysene (IV), the most mutagenic chrysene derivative in both systems, was 6- to 18-fold more active than the non-bay-region tetrahydroepoxide, 1,2-epoxy-1,2,3,4-tetrahydrochrysene. 1,2-Dihydrochrysene (V) was metabolized to highly mutagenic products, and both IV and V were as tumorigenic as chrysene on mouse skin. The diastereomeric bay-region diol-epoxides of phenanthrene exhibited dose-dependent mutagenic activity in ST, although they were less active than the corresponding bay-region diol-epoxides of chrysene. (\pm)-1 β ,2 α -Dihydroxy-3 α ,4 α -epoxy-1,2,3,4-tetrahydrophenanthrene (VI) was more mutagenic in ST TA100 and CHC than was its diastereomer, and the two diol-epoxides had low but equivalent activity in ST TA98. In both systems, the bay-region 3,4-epoxy-1,2,3,4-tetrahydrophenanthrene was 7- to 60-fold more mutagenic than was VI and 8- to 17-fold more mutagenic than 1,2-epoxy-1,2,3,4-tetrahydrophenanthrene. Neither phenanthrene nor its three metabolically possible *trans*-dihydrodiols were metabolized to bacterial mutagens by rat liver microsomes, and these compounds showed little or no tumor initiating activity on mouse skin. The bay-region tetrahydro-3,4-epoxide had significant tumorigenic activity on mouse skin. (29 refs)

- 79-6305 Comparative Mutagenicity, Tumor-initiating Activity, Carcinogenicity, and In Vitro Metabolism of Fluorinated 5-Methylchrysenes. (Eng) Hecht, S. S. (Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Dana Rd., Valhalla, NY 10595); LaVoie, E.; Mazzarese, R.; Hirota, N.; Ohmori, T.; Hoffmann, D. *J Natl Cancer Inst* 63(3): 855-861; 1979.

Seven monofluorinated 5-methylchrysene (5-MeC) derivatives were tested for mutagenicity in *Salmonella typhimurium* TA100 and for tumor-promoting and complete carcinogenic activity on mouse skin; in vitro metabolism in the presence of an activated rat liver homogenate was also investigated. The compounds studied were: 1-fluoro-5-methylchrysene (1-F-5-MeC), 3-fluoro-5-methylchrysene (3-F-5-MeC), 6-fluoro-5-methylchrysene (6-F-5-

MeC), 7-fluoro-5-methylchrysene (7-F-5-MeC), 9-fluoro-5-methylchrysene (9-F-5-MeC), 11-fluoro-5-methylchrysene (11-F-5-MeC), and 12-fluoro-5-methylchrysene (12-F-5-MeC). All seven compounds and 5-MeC were mutagenic toward TA100 in the presence of liver homogenates from F344 rats treated with Aroclor 1254; 7-F-5-MeC was the most mutagenic compound. 1-F-5-MeC and 3-F-5-MeC had significantly less tumor-initiating activity on the skin of Swiss mice than 5-MeC at both doses studied (30 and 100 μ g), whereas 12-F-5-MeC was less tumorigenic than 5-MeC only at 30 μ g. The other derivatives had as much tumor initiating activity as 5-MeC. In the tests of complete carcinogenicity, 1-F-5-MeC, 3-F-5-MeC, and 12-F-5-MeC showed no significant tumorigenicity. The only compound showing tumorigenic activity greater than that of 5-MeC was 6-F-5-MeC. The metabolic study showed that F substitution inhibited the oxidative metabolism at the position of attachment and at neighboring positions. Thus, for 12-F-5-MeC, a major activation pathway was blocked (formation of the 1,2-dihydrodiol); for 6-F-5-MeC, a detoxification pathway was inhibited. (20 refs)

- 79-6306 Multicellular Origin of Fibrosarcomas in Mice Induced by the Chemical Carcinogen 3-Methylcholanthrene. (Eng) Reddy, A. L. (Medical Genetics Section, Medical Service, Veterans Admin. Medical Center, Seattle, WA 98108); Fialkow, P. J. *J Exp Med* 150(4): 878-887; 1979.

The cellular origin of tumors induced by 3-methylcholanthrene (MCA) was investigated in mice with X-chromosome inactivation mosaicism. Male feral mice carrying the electrophoretic variant for the X-linked enzyme phosphoglycerate kinase (PGK type 1A) were bred with females from inbred strains homozygous for the usual *Pgk-1^b*. The F₁ hybrids heterozygous for the wild type and variant PGK genes (*Pgk-1^b/Pgk-1^a*) were given a single dose of MCA (0.2 mg or 2.0 mg sc). Five fibrosarcomas developing at the site of MCA injection were analyzed for the production of type A or type B isoenzyme or a combination of the two. Tumors with a clonal origin in *Pgk-1^b/Pgk-1^a* mice should display either B- or A-type PGK, whereas those with a multicellular origin may exhibit both B and A isoenzymes. Both B and A types of PGK (double-enzyme phenotypes) were found in each of the five tumors. However, single enzyme phenotypes were observed in at least one fragment from a single nodule in two tumors. The neoplasms had gross and histologic features typical of fibrosarcomas with anaplastic spindle-shaped cells and numerous mitoses. Chromosomes in cultured cells were examined at the second passage and almost every cell studied was hyperploid. The occurrence of a double-enzyme phenotype in each MCA-induced tumor strongly suggests a multicellular origin. (16 refs)

- 79-6307 Effect of Testosterone and 6-Hydroxydopamine Treatment on the Metabolism of Catecholamine and 5-Hydroxytryptamine in Methylcholanthrene-induced Prostate Carcinoma of Rats. (Eng) Rastogi, R. B. (Bio-Res. Labs., Ltd., 87 Senneville Road, Senneville, Montreal, Quebec, Canada); Agarwal, R. A.; Jande, S. S.; Singhal, R. L. *Can J Physiol Pharmacol* 57(6): 586-594; 1979.

The precursors tyrosine and tryptophan as well as the synthesizing and deaminating enzymes of catecholamines were identified in methylcholanthrene-induced prostatic carcinomas of Fischer rats. Tyrosine hydroxylase monoamine oxidase, catechol O-methyltransferase, dopamine, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid seemed to be neoplastic in origin, since

electron microscopic studies failed to reveal the presence of any neuronal elements in this squamous epithelial cell carcinoma. Castration of rats significantly reduced the activity of tyrosine hydroxylase and the levels of tyrosine, dopamine, tryptophan, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in prostate tumors. The changes appeared to be androgen-specific, since reinduction of testosterone restored several of these biochemical parameters virtually to control limits. Chemical sympathectomy induced by 6-hydroxydopamine failed to alter monoamine metabolism; however, the prostatic tumors grown in 6-hydroxydopamine-treated rats showed significantly (32%) less necrosis than those grown in normal animals. (33 refs)

- 79-6308 Tumorigenic Activity of 3-Methylcholanthrene Metabolites on Mouse Skin and in Newborn Mice. (Eng) Levin, W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110); Buening, M. K.; Wood, A. W.; Chang, R. L.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *Cancer Res* 39(9): 3549-3553; 1979.

3-Methylcholanthrene (MCA) and eight of its metabolites were tested for tumorigenic activity using two tumor models: female CD-1 mouse skin treated with 3-30 nanomoles (nmol) MCA as a single topical application followed 7 days later by twice weekly topical applications of 12-O-tetradecanoylphorbol-13-acetate for 30 wk; and newborn Swiss-Webster BLU:Ha mice given a total of 21 or 49 nmol MCA ip in increasing doses on days 1, 8, and 15 after birth. MCA, 2-hydroxy-MCA, MCA-2-one, and 1,9,10-trihydroxy-9,10-dihydro-MCA were approx equipotent as tumor initiators on mouse skin. 1-Hydroxy-MCA was approx one fourth as active, and MCA-1-one and *trans*-11,12-dihydroxy-11,12-dihydro-MCA showed no significant activity. 1,9,10-Trihydroxy-9,10-dihydro-MCA was the most active compound in inducing pulmonary tumors in newborn mice, MCA and MCA-2-one showing approx one third to one half of this activity, and 2-hydroxy-MCA showing slightly less activity than the latter two. 1-Hydroxy-MCA had marginal activity in this model; and MCA-11,12-oxide, *trans*-11,12-dihydroxy-11,12-dihydro-MCA, and MCA-1-one were inactive. The high tumorigenicity of 1,9,10-trihydroxy-9,10-dihydro-MCA in both models suggests bay-region activation of MCA to an ultimate carcinogen. The data also suggest that other metabolites of MCA may play a role in the carcinogenicity of this compound. (32 refs)

- 79-6309 The Initiation of Tumours on Mouse Skin by Dihydrodiols Derived from 7,12-Dimethylbenz[a]anthracene and 3-Methylcholanthrene. (Eng) Chouroulinkov, I. (Institut de Recherches Scientifiques sur le Cancer, B. P. No. 8, 94800 Villejuif, France); Gentil, A.; Tierney, B.; Grover, P. L.; Sims, P. *Int J Cancer* 24(4): 455-460; 1979.

The *cis*-2a,3-diol and the *trans*-4,5-, *trans*-7,8-, *trans*-9,10- and *trans*-11,12-dihydrodiols of 3-methylcholanthrene and the *trans*-3,4-, *trans*-5,6-, *trans*-8,9- and *trans*-10,11- dihydrodiols of 7,12-dimethylbenz[a]anthracene were compared with the parent hydrocarbons for their abilities to initiate skin tumors in female CD1 mice. Groups of mice received a single topical application (25 µg) of a diol or of a hydrocarbon, and 1 wk later repeated topical applications (1 µg) of 12-O-tetradecanoylphorbol-13-acetate were commenced. The diols capable of being converted into bay-region vicinal diol-epoxides, ie the 9,10-diol of 3-methylcholanthrene and the 3,4-diol of 7,12-dimethylbenz[a]anthracene were active as initiating agents, but no more so than their parent hydrocarbons.

The K-region 5,6-diol of 7,12-dimethylbenz[a]anthracene, which cannot be converted directly into a vicinal diol-epoxide, was also active as a tumor-initiating agent when applied to mouse skin. (29 refs)

- 79-6310 Biochemical and Immunological Characteristics of Tumor Specific Antigens on Chemically Induced Rat Tumors. (Eng) Baldwin, R. W. (Cancer Res. Campaign Labs., Univ. Nottingham, Univ. Park, Nottingham NG7 2RD, England); Price, M. R.; Moore, V. E. In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, R. W., ed. (New York: Elsevier): 590 pp.; 11-24; 1978.

The current status of research into the isolation and characterization of tumor-specific antigens associated with 3-methylcholanthrene (3-MC)-induced sarcomas (MC7 and MC4) and 4-dimethylaminoabobenzene (DAB)-induced hepatomas (D23) in adult WAB/Not rats is reviewed. Antibody specific for D23 and MC7 sarcoma was absorbed only by intact cells and plasma membrane-containing fractions, and immunization of syngeneic rats with extranuclear membrane (ENM) and plasma membrane preparations from sarcoma MC7 indicated that these membrane fractions contained tumor-specific antigen. Solubilization of the membrane-associated antigen required relatively vigorous treatment, including 3 M KCl extraction of tumor homogenates or solubilization of membrane preparations with papain or EDTA. The protein profiles of the fractionated extracts from hepatoma D23 and sarcoma MC4 on ion-exchange chromatograms were markedly similar, as were the regions with which antigenic activities were associated. Gel-filtration chromatography of papain extracts of hepatoma D23 showed that antigenic activity was associated with material eluting with a mol wt of approx 55,000. Specific immunoabsorption techniques applied to the sarcoma MC7 model showed that all antigenic activity resided in a high-mol-wt fraction, and gel electrophoresis of this material showed two major protein bands with approx mol wts of 75,000 and 42,000, respectively. These fractions were immunogenic in syngeneic rats, and the immunoabsorbent-purified fraction from 3 M KCl extracts of sarcoma MC7 elicited a tumor-specific antibody response *in vivo*. However, tumor growth was enhanced rather than suppressed in rats preimmunized with the sarcoma MC7 antigen preparation in Freund's complete adjuvant. (27 refs)

- 79-6311 Effect of Thymosine on Oxidative Phosphorylation in Rat Liver Mitochondria during Chemical Carcinogenesis. (Rus) Grynevych, Iu. A. (Roentgeno-Radiologica and Oncological Inst., Kiev, USSR); Alferov, A. N.; Dziubko, N. Ia.; Chebotarev, V. F. *Ukr Biokhim Zh* 51(3): 255-258; 1979.

The effect of thymosine (TM) on oxidative phosphorylation in liver mitochondria was studied in CBA mice. The animals were inoculated sc with 50 mg/kg 20-methylcholanthrene and sacrificed 10, 30, 50 or 130 days later. Five days prior to sacrifice, rats were immunized with sheep RBC (5×10^9), and 1 day prior to immunization, they received a single ip injection of 5 mg TM. A significant inhibition of oxidative phosphorylation was first recorded on day 50 of carcinogen administration (0.136 unit, compared with 0.162 unit on day 30, 0.183 unit on day 10, and 0.189 unit in controls). Max inhibition of oxidative phosphorylation was observed on day 130 of carcinogenesis (0.110 unit). Administration of TM during the early period of carcinogenesis (up to day 50) enhanced the rate of oxidative phosphorylation (0.198 unit). TM administration on

day 129 of carcinogenesis did not prevent the inhibition of oxidative phosphorylation (0.140 unit). (14 refs)

- 79-6312 Microsomal and Nuclear Metabolism of 3-Methylcholanthrene. (Eng) Tierney, B. (Dept. Biochemistry, Univ. Vermont Sch. Medicine, Burlington, VT 05405); Bresnick, E.; Sims, P.; Grover, P. L. *Biochem Pharmacol* 28(17): 2607-2610; 1979.

Hepatic nuclei and microsomes prepared from rats pretreated with 3-methylcholanthrene 3-MC, 20 mg/kg body wt as well as hepatic nuclei from untreated rats were incubated with generally ^3H -labeled 3-MC (50 μCi plus 0.1 μmole cold 3-MC in acetone) in the presence of an NADPH-generating system. The metabolic products formed by these three systems were analyzed by high pressure liquid chromatography and were found to be comparable both qualitatively and quantitatively. The metabolic formation, from both nuclei and microsomes, of radioactive products corresponding to the *cis*-1,2- and 11,12-diol, the *trans*-4,5-, 9,10-, and 11,12-dihydrodiol, and the 1- and 2-hydroxy and 1- and 2-ketone derivatives of 3-MC was observed when these metabolites were compared on high pressure liquid chromatographs with authentic compounds. Pretreatment of the rats with 3-MC resulted in a marked increase in nuclear metabolism, particularly in the formation of 2-hydroxy-3-methylcholanthrene. These studies further reinforce the importance of the nucleus in the metabolic activation of polycyclic hydrocarbons. (31 refs)

- 79-6313 Induction, Inhibition, and Biological Properties of Aryl Hydrocarbon Hydroxylase in a Stable Human B-Lymphocyte Cell Line, RPMI-1788. (Eng) Freedman, H. J. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., New York, NY 14263); Parker, N. B.; Marinello, A. J.; Gurtoo, H. L.; Minowada, J. *Cancer Res* 39(11): 4612-4619; 1979.

The induction and inhibition of aryl hydrocarbon hydroxylase (AHH) by various chemicals in a stable, human B-lymphocyte cell line (RPMI-1788) are reported, together with the kinetic and biological properties of the enzyme in these cells. Over the dose ranges tested and on molar basis the inducers, in decreasing order of potency, were 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, dibenz(*a,h*)-anthracene, 3-methylcholanthrene, benzo(*a*)pyrene, and 1,2-benzanthracene. Potential inducers that, paradoxically, diminished basal AHH included 7,12-dimethylbenzanthracene, 2,5-diphenyloxazole, and chrysene. Induction under optimal culture conditions ensured maximal activities three- to fourfold above basal AHH. The characteristics of the induced [dibenz(*a,h*)-anthracene] and basal enzymes were identical. Both had similar pH curves (optima at 8.25) and inhibitor specificity (α - and β -naphthoflavones, metyrapone, and 2-diethylaminoethyl-2,2-diphenylvalerate in decreasing potency). Induced and basal enzymes exhibited similar half-lives (41 and 46 hr), apparent activation energies (16.7 and 16.6 kcal/mol), temperature optima (37-38 C and 38-39 C), temperature-dependence of denaturation (range, 42-50 C), and apparent K_m with benzo(*a*)pyrene (1.8 and 0.8 μM). The small difference in the apparent K_m was related to enzyme concentration in the incubation medium rather than to the quality of the enzyme. (56 refs)

- 79-6314 Ovarian Aryl Hydrocarbon Hydroxylase Activity and Primordial Oocyte Toxicity of Polycyclic Aromatic

Hydrocarbons in Mice. (Eng) Mattison, D. R. (Reproductive Toxicology Unit, Pregnancy Res. Branch, Natl. Inst. Child Health and Human Development, NIH, Building 10, Room 13N266, Bethesda, MD 20014); Thorgiersson, S. S. *Cancer Res* 39(9): 3471-3475; 1979.

Mouse ovarian aryl hydrocarbon hydroxylase (AHH) activity was measured in control mice and in DBA/2N (D2) and C57BL/6N (B6) mice treated with 3-methylcholanthrene (3-MC). Basal ovarian AHH activity was similar in both strains (3 picomoles/mg/min). Ovarian AHH was induced two to threefold in B6 mice after 3-MC treatment, but no change was observed in similarly treated D2 mice. Primordial oocytes of both D2 and B6 mice were destroyed by the carcinogenic polycyclic aromatic hydrocarbons (PAH) 3-MC, benzo(*a*)pyrene (BP), and 7,12-dimethylbenz(*a*)anthracene (DMBA), but not by the non-carcinogens pyrene, α -naphthoflavone, and β -naphthoflavone. The rate of primordial oocyte destruction after PAH administration was faster in responsive B6 mice than in nonresponsive D2 mice. After a single ip injection of PAH (80 mg/kg), 50% of the oocytes were destroyed by the following times: DMBA, 1 day for B6, 2 days for D2; 3-MC, 2-3 days for B6, 6 days for D2; BP, 2-3 days for B6, 12 days for D2. Dose-response curves of DMBA, 3-MC, and BP also indicated greater primordial oocyte toxicity in responsive B6 mice than in nonresponsive D2 mice. The threshold dose for oocyte destruction 5 days after PAH injection was: DMBA, <1 mg/kg for B6, <2.5 mg/kg for D2; 3-MC, <5 mg/kg for B6, approx 80 mg/kg for D2; BP, <5 mg/kg for B6, approx 80 mg/kg for D2. In 3-MC-treated D2B6F₁ x D2 backcross mice, PAH-inducible ovarian AHH activity and rapid primordial oocyte toxicity cosegregated with inducible hepatic AHH activity. Primordial oocyte toxicity was blocked by simultaneous treatment with α -naphthoflavone. The relative toxicity of the carcinogens to primordial oocytes in both D2 and B6 mice was DMBA > 3-MC > BP. (21 refs)

- 79-6315 Metabolism of Benzo(*a*)pyrene, *N*-Nitrosodimethylamine, and *N*-Nitrosopyrrolidine and Identification of the Major Carcinogen-DNA Adducts Formed in Cultured Human Esophagus. (Eng) Harris, C. C. (Lab. Experimental Pathology, Building 37, Room 3A07, NCI, Bethesda, MD 20205); Autrup, H.; Stoner, G. D.; Trump, B. F.; Hillman, E.; Schafer, P. W.; Jeffrey, A. M. *Cancer Res* 39(11): 4401-4406; 1979.

Cultured nontumorous esophageal explants from two patients with esophageal carcinoma and six autopsy cases were exposed to [^3H]benzo(*a*)pyrene (BP: 1.5 μM), [^{14}C]N-nitrosodimethylamine (DMN: 100 μM) or [^{14}C]Nitrosopyrrolidine (NPY: 100 μM) for 24 hr. Radioactivity was found bound to both mucosal protein (BP, DMN, and NPY) and DNA (BP and DMN). The major DNA-carcinogen adducts were: (1) with BP, N²-[10 β -7 β , 8 α , 9 α -trihydroxy-7,8,9, 10-tetrahydrobenzo(*a*)pyrenyl] deoxyguanosine; and (2) with DMN, 7-methylguanine and O⁶-methylguanine (ratio of O⁶- to 7-methylguanine was 0.3). The interindividual variations among the samples in binding levels to mucosal DNA were 99-fold for BP and 10-fold for DMN. Both organic solvent-extractable and water-soluble metabolites (sulfate esters, 21%-55%; glucuronide conjugates, 7%-37%; and glutathione conjugates, 24%-66%) were detected in the culture medium. The proximate carcinogenic metabolite of BP, (-)-*trans*-7,8-dihydro-7,8-dihydroxybenzo(*a*)pyrene was detected in the organic solvent-extractable fraction. Analysis of the patterns of both water-soluble and organic solvent-extractable metabolites revealed only minor qualitative differences. These results provide

evidence that the human esophagus has the metabolic capacity to activate the environmental chemical procarcinogens BP and DMN into electrophilic metabolites that bind to DNA and protein. (31 refs)

- 79-6316 The Epoxide Hydratase Inducer Trans-Stilbene Oxide Shifts the Metabolic Epoxidation of Benzo(a)pyrene from the Bay- to the K-Region and Reduces Its Mutagenicity. (Eng) Buckner, M. (Section on Biochemical Pharmacology, Inst. Pharmacology, Univ. Mainz, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany); Golan, M.; Schmassmann, H. U.; Glatt, H. R.; Stasiecki, P.; Oesch, F. *Mol Pharmacol* 16(2): 656-666; 1979.

Adult male Sprague-Dawley rats were injected with trans-stilbene oxide (TSO; 2 mmole/kg/day, ip, for three days) and were sacrificed 24 hr later. The following parameters were determined in liver microsomes prepared from TSO-treated rats and controls: monooxygenase and epoxide hydratase activities, and benzo(a)pyrene (BP) metabolite profile and mutagenicity. Epoxide hydratase activity was increased 3-fold and ethoxycoumarin O-deethylase activity 2.5-fold in liver microsomes from TSO-treated rats. (¹⁴C)-BP was incubated with control and with TSO-treated rat liver microsomes and the metabolites separated by high pressure liquid chromatography. The total number of metabolites was not significantly increased after TSO-treatment; but the quantity of metabolites which were oxidized at the benzo ring was greatly decreased, and the K-region metabolites were increased. A much higher percentage of the BP 4,5-oxide was converted to the corresponding dihydrodiol by TSO-induced microsomes compared with controls. Pretreatment of the rats with TSO strongly decreased mutagenicity of BP activated by liver microsomes for *Salmonella typhimurium*. Thus, the two effects of TSO, shift of the site of metabolic oxidation and induction of epoxide hydratase, synergistically provided protection against the mutagenic effects of BP. The changes in BP metabolites occurred without any significant changes in the BP monooxygenase activity, indicating that measurements of aryl hydrocarbon hydroxylase activity do not always correlate with the toxic effects of polycyclic aromatic hydrocarbons. (32 refs)

- 79-6317 Photoelectric Properties and Detection of the Aromatic Carcinogens Benzo(a)pyrene and Dimethylbenzanthracene. (Eng) Houle, W. A. (Dept. Chemistry, Univ. Oregon, Eugene, OR 97403); Brown, H. M.; Griffith, O. H. *Proc Natl Acad Sci USA* 76(9): 4180-4184; 1979.

The absolute photoelectron quantum yield spectra for benzo(a)pyrene (BP) and dimethylbenzanthracene (DMBA) were investigated in the wavelength range 180-230 nanometers (nm). These polycyclic aromatic carcinogens had photoelectron quantum yields of approx 2×10^{-3} electrons per incident photon at 180 nm. The quantum yields fell off quickly and monotonically at wavelengths longer than 210 nm [5.9 electron volts (eV)]. Threshold values for BP and DMBA were 5.25 ± 0.06 eV and 5.17 ± 0.04 eV, respectively. The photoelectron quantum yields of BP and DMBA were several orders of magnitude greater than those of typical components of biological membranes (amino acids, phospholipids, and polysaccharides). Preliminary micrographs of BP and DMBA sublimed onto poly(L-lysine) and onto dimyristoyl phosphatidylcholine demonstrated the high contrast of small crystallites of carcinogens against a background of membrane components. These results and calculations involving relative contrast factors suggest that the distribution of these carcinogens in

biological membranes can be determined by using photoelectron microscopy. (27 refs)

- 79-6318 Genetic Differences in the Metabolic Activation of Benzo(a)pyrene in Mice. Attempts to Correlate Tumorigenesis with Binding of Reactive Intermediates to DNA and with Mutagenesis In Vitro. (Eng) Pelkonen, O. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014); Boobis, A. R.; Levitt, R. C.; Kouri, R. E.; Nebert, D. W. *Pharmacology* 18(6): 281-293; 1979.

An attempt was made to correlate genetic differences in the carcinogenesis index of sc benzo(a)pyrene (BP)-initiated fibrosarcomas with specific genetic differences in any single chromatographic peak, representing a BP metabolite-nucleoside complex, and with specific genetic differences in BP mutagenicity to *Salmonella typhimurium*. The carcinogenesis index in the genetically responsive C3H inbred mouse strain was > fivefold higher and 15-fold higher than in the responsive C57BL/6 and the nonresponsive DBA/2 strains, respectively. Carcinogenesis indices involving F₁ hybrids of these strains indicated that additional genes other than the Ah locus may cause a particular inbred strain to be more resistant, or sensitive, to polycyclic hydrocarbon-initiated tumors than expected solely on the basis of aryl hydrocarbon hydroxylase (AHH) inducibility. The DNA-bound BP metabolite complexes generated by mouse liver or skin microsomes in vitro were resolved into nine chromatographic peaks. Eight peaks, shown previously to be associated with increased hepatic cytochrome P-450 content, were greater with liver microsomes from C3H and C57BL/6 mice and the (C57BL/6)(C3H)F₁, (C3H)(DBA/2)F₁, and (C57BL/6)(DBA/2)F₁ hybrids than from the DBA/2 strain. All nine peaks were greater with skin microsomes in vitro from C3H and C57BL/6 than from DBA/2 mice. BP mutagenicity with *Salmonella* strain TA98 was increased five- to sixfold with liver microsomes from methylcholanthrene-treated C3H and C57BL/6 mice and the three F₁ hybrids, compared with liver microsomes from DBA/2 mice. The data demonstrate a good correlation between genetically determined increases in the in vitro endpoints investigated but not between these two parameters and the carcinogenesis index. (32 refs)

- 79-6319 The Relationship Between Sister Chromatid Exchange, Chromosome Aberration and Gene Mutation Induction by Several Reactive Polycyclic Hydrocarbon Metabolites in Cultured Mammalian Cells. (Eng) Connell, J. R. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks, HP8 4SP, England). *Int J Cancer* 24(4): 485-489; 1979.

The ability of three ultimate metabolites of benzo(a)pyrene as well as of 7-bromomethylbenz(a)anthracene to induce 8-azaguanine mutants, sister-chromatid exchanges, and chromosome aberrations was investigated. 7 β ,8 α -Dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydro-benzo(a)pyrene was an extremely efficient inducer of mutants and sister-chromatid exchanges at 100% survival, whereas its geometrical isomer, 7 β ,8 α -dihydroxy-9 β ,10 β -epoxy-7,8,9,10-tetrahydro-benzo(a)pyrene, and benzo(a)pyrene-4,5-oxide were comparatively weak. The potency of this compound, as both a mutagen and a sister-chromatid exchange inducer, gives further evidence that it may be the important carcinogenic metabolite of benzo(a)pyrene. 7-Bromomethylbenz(a)anthracene was a moderate mutagen and inducer of sister chromatid exchanges.

Comparisons of the relative potencies of these four chemicals as inducers of both mutations and sister chromatid exchanges indicate that these two phenomena are not directly related. The induction of sister chromatid exchanges also appears to be independent of the induction of chromosome aberrations. (23 refs)

- 79-6320 Normal and Benzo(a)pyrene-transformed Fetal Mouse Brain Cells. II. Ultrastructural Study. (Eng) Tripiet, M. F. (Unité de Cancerologie Experimentale, 27 Boulevard Leï'Roure F-13009, Marseille, France); Markovits, P.; Papadopoulos, D.; Toga, M. *Acta Neuropathol (Berl)* 47(3): 205-211; 1979.

Normal and benzo(a)pyrene (BaP: 0.02%)-transformed brain cells from 14-day-old A/J and C3H mouse fetuses were examined ultrastructurally. Control cultures of whole brain cells were of three types: pale, multipolar cells resembling differentiated glial cells, with abundant cytoplasm and elongated processes; rounded, large cells, which were similar to poorly differentiated glial cells; and elongated, apparently nondifferentiated cells that could correspond to spongioblastic cells. In BaP-treated whole brain cultures, some cells appeared similar to mature glial cells and were rich in gliofilaments, which were arranged in dense bundles. Other cells were small and star-shaped, with very long cell processes. Some puncta adherentia-type junctions were observed between plasma membranes. Control fetal cortex cells were oval or rounded with processes and were probably relatively immature neuroglia. The BaP-treated cortex cells were variable in shape and frequently multipolar with long fine processes. No virus particles were observed. (23 refs)

- 79-6321 Normal and Benzo(a)pyrene-transformed Fetal Mouse Brain Cells. I. Tumorigenicity and Immunohistochemical Detection of Glial Fibrillary Acidic Protein. (Eng) Markovits, P. (Section de Biologie, Institut Curie, 26, rue d'Ulm, F-75231 Paris Cedex 05, France); Maunoury, R.; Tripiet, M. F.; Coulomb, B.; Levy, S.; Papadopoulos, D.; Vedrenne, C.; Benda, P. *Acta Neuropathol (Berl)* 47(3): 197-203; 1979.

Morphology, tumorigenicity, and the presence of glial fibrillary acidic protein (GFAP) were studied in normal and benzo(a)pyrene (BaP: 0.02%)-treated brain cells taken from 14-day-old A/Jax or C3H mouse fetuses. Control cultures of cortex remained non-transplantable for up to 14 passages, whereas spontaneous transformation occurred after 11 passages of control whole brain cultures. The latter cultures were tumorigenic in A/Jax mice. After seven to eight passages, malignant transformation was observed in BaP-treated whole brain and cortex cultures. These cells induced tumor formation when injected sc in nude C3H, but not A/Jax, mice with an av latency of 20 (cortex) or 53 (whole brain) days. The induced tumors contained fusiform cells that tended to be arranged in bundles. GFAP was detected in almost all untreated and BaP-treated cultures, although it seemed to be lost from some chemical-treated cortex cultures after 14-16 passages. GFAP was also regularly detected in the tumors induced by transformed cells in nude and A/Jax mice. The data indicate that glia-like cells persist after a long period of maintenance in vitro and transformation. (24 refs)

- 79-6322 Effects of Various In Vitro Inhibitors of Benzo(a)pyrene Metabolism in Isolated Rat Lung

Perfusion. (Eng) Vahakangas, K. (Dept. Pharmacology, Univ. Oulu, Oulu 22, Finland); Nevasaari, K.; Pelkonen, O.; Karki, N. T. *Acta Pharmacol Toxicol (Copenh)* 45(1): 1-8; 1979.

Various in vitro inhibitors of benzo(a)pyrene (BP) metabolism were added with ^3H -BP to fluids used to perfuse isolated rat lung to see whether their effects are dependent on the integrity of the tissue. ^3H -BP and its metabolites were measured by thin-layer chromatography and radiometry in both samples of perfusion medium and homogenates of lung tissue. The total covalent binding to lung tissue was used as a measure of the formation of reactive metabolites. In methylcholanthrene-induced rat lung, BP metabolism was inhibited significantly by α -naphthoflavone (an inhibitor of monooxygenase) and, to a lesser degree, by diethyl maleate (an inhibitor of glutathione), salicylamide (an inhibitor of conjugases), and, surprisingly, by D-saccharo-1,4-lactone (an inhibitor of β -glucuronidase). With trichloropropene oxide, which inhibits epoxide hydratase, the metabolism was either decreased or unchanged. Nicotine had no effect on BP metabolism. Nicotine and diethyl maleate significantly increased and α -naphthoflavone and salicylamide decreased the covalent binding of radioactivity to lung tissue. In most cases, the changes in BP metabolism observed during perfusion were due to the effects of modifiers on the enzyme systems. (15 refs)

- 79-6323 Mutagenic Effects of Benzo(a)pyrene after Metabolic Activation by Hepatic 9000 g Supernatants or Intact Hepatocytes. (Eng) Brouns, R. E. (Inst. Pharmacology and Toxicology, Univ. Nijmegen, Nijmegen, Netherlands); Bos, R. P.; van Gemert, P. J.; Yih-van de Hurk, E. W.; Henderson, P. T. *Mutat Res* 62(1): 19-26; 1979.

The effects of isolated rat hepatocytes and the 9,000-g supernatant from these cells on the mutagenicity of benzo(a)pyrene (BP) toward *Salmonella typhimurium* TA100 were investigated. BP was not mutagenic in the cell-mediated assay unless the hepatocytes were disrupted after they were preincubated with BP or the intracellular glutathione content was reduced. A retention of active metabolites and an effective detoxication may account for the absence of a mutagenic response. (14 refs)

- 79-6324 Theoretical Model Study of the Reactivity of Benzo(a)pyrene Diol Epoxide with the Amino Groups of the Nucleic Acid Bases. (Eng) Lavery, R. (Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Theorique associe au C.N.R.S., 13 rue P. et M. Curie, F-75005 Paris, France); Pullman, B. *Int J Quantum Chem* 16(1): 175-188; 1979.

A quantum-mechanical model study, aided by classical potential calculations, was made of the formation of adducts between the candidate ultimate carcinogen benzo(a)pyrene diol epoxide (BPDE) and the amino groups of guanine, adenine, and cytosine. Considerably less steric hindrance occurs for adducts or intermediates if the metabolized ring of BP adopts a B(I) (boat) or an HC(I) (half-chain) conformation. The quantum-mechanical studies of adducts between the nucleic acid bases and an allyl cation, modeling BPTC (the triol carbonium ion derived from BPDE), suggest that rapid formation of an addition product at the base amino group would occur for guanine, adenine, and cytosine. However, when this intermediate is deprotonated, in an endothermic and slower step, to yield the final adduct, guanine is clearly favored over adenine and cytosine. This result is proposed as at least a partial explanation of the predominance of guanine adducts

when nucleic acids are exposed to BPDE. In a preliminary study of the approach of the BP metabolite toward a five-base pair fragment of B-DNA, it was demonstrated that the minor groove, which contains the guanine amino group, causes more steric hindrance as the BP metabolite approaches than does the major groove, which contains the adenine and cytosine amino groups. (26 refs)

- 79-6325 Benzo(a)pyrene Quinone Metabolism in Tracheal Organ Cultures. (Eng) Mass, M. J. (Dept. Pathology, Univ. North Carolina Sch. Medicine, Chapel Hill, NC 27514); Kaufman, D. G. *Biochem Biophys Res Commun* 89(3): 885-892; 1979.

The hypothesis that benzo(a)pyrene quinones (BP quinones) can be further metabolized by tracheal organ cultures was tested with the use of Syrian golden hamster tracheas. The tracheal organ cultures metabolized a mixture of BP quinones into products that were not extracted with acetone/ethyl acetate and were water-soluble. When the culture medium was extracted of organic-soluble metabolites and the water-soluble metabolites were exposed to β -glucuronidase, BP quinones and an unidentified highly polar metabolite were released. When the results were evaluated quantitatively, it was found that 30% of the water-soluble metabolites were glucuronide conjugates. The remaining 70% of the aqueous soluble radioactivity was not sensitive to β -glucuronidase and was not identified. When BP was used as the substrate in tracheal organ culture, treatment of the aqueous soluble metabolites with β -glucuronidase resulted in the release of some BP quinones. It has previously been assumed that BP quinones are "end-products" of BP metabolism; however, this report demonstrates that BP quinones are subject to further metabolic processes. (17 refs)

- 79-6326 Mutagenicity of Soot and Associated Polycyclic Aromatic Hydrocarbons to *Salmonella typhimurium*. (Eng) Kaden, D. A. (Dept. Nutrition, Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Hites, R. A.; Thilly, W. G. *Cancer Res* 39(10): 4152-4159; 1979.

The mutagenic activities of the polycyclic aromatic hydrocarbon (PAH)-containing fractions of several soot samples were measured in *Salmonella typhimurium* strain TM677, using resistance to 8-azaguanine as a genetic marker. Exponentially growing bacterial cultures were exposed to the test agents for 2 hr in the presence of postmitochondrial supernatant, prepared as a 25% liver homogenate of phenobarbital (PB)- or Aroclor (AC)-pretreated male Sprague-Dawley rats. The methylene chloride extracts of nitrogen-containing, sulfur-containing, furnace black, and kerosene soots were 10%-17% as mutagenic as pure benzo(a)pyrene (BP) at concentrations of 20-50 μ g/ml and in the presence of S9 from AC-pretreated rats. Significantly higher concentrations of soot extract or BP were needed to induce significant mutation in the presence of S9 from PB-pretreated rats. The observed mutagenicities of the soot extracts could not be explained by the mutagenicity of BP, and strictly additive mutagenicity was observed when BP was added to nitrogen-containing soot extract. Of 70 PAH components of the soots, 34 induced a significant increase in 8-azaguanine resistance, and 3 of the remaining 36 showed possible low-level mutagenicity. Three PAH, perylene, cyclopenta(c,d)pyrene, and fluoranthene, exhibited greater mutagenicity than BP at equimolar concentrations. The mutagenic

activity of a given PAH was often lower than that of the corresponding aza compound. The mutagenic activity of the PAH fraction of the kerosene soot extract appeared to be due to simple additive contributions of its mutagenic components. (32 refs)

- 79-6327 Anticarcinogenic Effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin or Benzo(a)pyrene and 7,12-Dimethylbenz(a)anthracene Tumor Initiation and Its Relationship to DNA Binding. (Eng) Cohen, G. M. (Dept. Biochemistry, Univ. Surrey, Guildford, GU2 5XH, Surrey, England); Bracken, W. M.; Iyer, R. P.; Berry, D. L.; Selkirk, J. K.; Slaga, T. J. *Cancer Res* 39(10): 4027-4033; 1979.

The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) pretreatment on the skin carcinogenicity of both benzo(a)pyrene [B(a)P] and dimethylbenz(a)anthracene (DMBA) was investigated in female Sencar mice. The topical administration of 1 μ g 72 hr prior to B(a)P (100 nanomol) or DMBA (10 nanomol) strongly inhibited tumor initiation by both agents. TCDD caused a marked decrease in the in vivo covalent binding of DMBA to DNA and RNA but significantly increased in vivo binding of B(a)P to DNA, with relatively little change in RNA binding. The in vivo binding of B(a)P to DNA in the absence of TCDD pretreatment was accompanied by formation of a major hydrocarbon-deoxyribonucleoside adduct, which cochromatographed with 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene bound to the exocyclic amino group of guanine. The increased in vivo binding to DNA following pretreatment with TCDD did not result in the formation of detectable amounts of this adduct but did result in the formation of other, as yet unidentified, adducts. The authors suggest that the absence of the adduct of 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene bound to guanine corresponds to the marked tumor-inhibitory properties of TCDD and that formation of this adduct may be a critical step in B(a)P-induced mouse skin carcinogenesis. (49 refs)

- 79-6328 Metabolism of Benzo(a)pyrene and the Related Enzyme Activities in Hamster Embryo Cells. (Eng) Hirakawa, T. (Dept. Physiological Chemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan); Nemoto, N.; Yamada, M.; Takayama, S. *Chem Biol Interact* 25(2/3): 189-195; 1979.

The rate of metabolism of benzo(a)pyrene (BP) and changes in related enzyme activities in cultured hamster embryo cells during successive subculture were studied. The activity of aryl hydrocarbon hydroxylase (AHH) was highest when embryo cells were first dispersed in tissue culture flasks and decreased during subsequent passages. On the other hand, uridine diphosphate (UDP)-glucuronyl transferase activity increased gradually during successive subculture. Treatment of the cells with 13 nanomol/ml of benz(a)anthracene (BA) for 24 hr increased the activity of AHH but not that of UDP-glucuronyl transferase. The metabolism of BP was measured in cells of the passages 1, 3 and 7. Metabolism of BP was most efficient in cells in passage 3; and the formation by passage 3 cells of glucuronic acid conjugates of BP, which are among the major metabolites found in the medium, was 3- and 10-fold more than those of cells in passages 1 and 7, respectively. Analysis of BP metabolites extracted from the medium with ethylacetate showed that the main metabolites were 9,10-diol and 7,8-diol. Phenols and quinones were released by treatment of the medium with β -glucuronidase, and their amounts were larger than those of diols at all passages. These results show that in hamster

embryo cells in early passages, BP is metabolized to conjugates of phenols with glucuronic acid. (15 refs)

- 79-6329 **Metabolic Inactivation of Reactive Metabolites.** (Eng) Oesch, F. (Inst. Pharmacology, Section Biochemical Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany). *Adv Pharmacol Ther* 9: 63-70; 1979.

Benzo(a)pyrene (BP), a compound composed exclusively of aromatic rings, was studied as a model for the mutagenic effects of the aromatic and olefinic moieties of more complex molecules. Chemicals possessing several fused aromatic rings and an angular structure are metabolized to many derivatives. Several of these derivatives are mutagenic but contribute very little to the total mutagenicity of the compound, the two major groups of mutagenically reactive metabolites being monofunctional arene oxides and dihydrodiol epoxides. The monooxygenase forms that are present will in part determine whether BP is predominantly epoxidized at the 4,5-position (monofunctional epoxide) or at the 7,8,9,10-position (dihydrodiol epoxide). A further contributing factor is the relative monooxygenase activity, higher activity favoring the reaction necessary for dihydrodiol epoxide formation. In metabolic situations in which monofunctional arene oxides represent the majority of the mutagenically reactive metabolites, epoxide hydratase efficiently inactivates, whereas if dihydrodiol epoxides predominate, it does not. In the latter situation, another enzyme was found that exerts protective effects complementary to those of epoxide hydratase dihydrodiol dehydrogenase. After the appearance of the primary lesion, differences in repair capacity and other host defense mechanisms will also contribute to differences in toxic manifestations. (25 refs)

- 79-6330 **Carcinogenicity and Polarographic Behaviour of Dibenzo[a,h]pyrene, 4,11-Diazadibenzo[a,h]pyrene and 7,14-Diazadibenzo[a,h]pyrene.** (Eng) Bahna, L. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Podany, V.; Benesova, M.; Godal, A.; Dufour, M.; Jacquignon, P.; Vachalkova, A. *Neoplasma* 26(1): 23-28; 1979.

The comparative carcinogenic activities of dibenzo[a,h]pyrene (I), 4,11-diazadibenzo[a,h]pyrene (II), and 7,14-diazadibenzo[a,h]pyrene (III) were studied in random-bred female Wistar rats following sc implantation of paraffin discs containing approx 10 mg of test chemical. Twenty-three local tumors were induced in animals implanted with I, compared with 16 local tumors in those treated with II and no local tumors in those treated with III. Tumor induction time was longer in the animals given II than in those given I. All tumors were sarcomas. The tumorigenicity of I and II was proportional to their electron donation and inversely proportional to their electron acceptance. Judging only by the oxidation potential of III, this compound need not necessarily be wholly inactive as a carcinogen. One reason for its observed inactivity might be that the nitrogen atoms occupying its *meso* region exclude the reaction(s) that would otherwise take place in this region in the parental hydrocarbon (I) during the development of its carcinogenic activity. (11 refs)

- 79-6331 **Large Interindividual Variations in Metabolism of Benzo(a)pyrene by Peripheral Lung Tissue from Lung Cancer Patients.** (Eng) Cohen, G. M. (Dept. Biochemistry, Univ.

Surrey, Guildford GU2 5XH, Surrey, England); Mehta, R.; Meredith-Brown, M. *Int J Cancer* 24(2): 129-133; 1979.

The metabolism of benzo(a)pyrene (BP) in short-term organ cultures of lung tissue from six patients with lung cancer was studied. After a 24-hr incubation of radiolabeled BP with lung tissue, 34.6%-74.8% of the initial radioactivity remained in the medium. Of this radioactivity, 24.7%-55.7% was associated with ethyl acetate-soluble materials and 6.7%-42.4% was associated with water-soluble materials. When the ethyl acetate-soluble radiolabeled material was separated by high-pressure liquid chromatography, metabolites chromatographing with 9,10-dihydro-9,10-dihydroxy-BP or (7/8,9)-trihydroxy-7,8,9,10,10-pentahydro-BP were observed. Two other major peaks corresponded to tetrahydrotetrahydroxy-BP's and more-polar metabolites. There was a 44-fold variation in the amount of BP remaining unmetabolized in the medium; this ranged from 1% in a culture obtained from one patient to 96.2% in a culture obtained from another. The data strongly suggest that there may be little basis for screening humans for variations in lymphocyte aryl hydrocarbon hydroxylase activity as a means of assessing their susceptibility to lung cancer. (23 refs)

- 79-6332 **Metabolism and Macromolecular Binding of the Carcinogen Benzo(a)pyrene and Its Relatively Inert Isomer Benzo(e)pyrene by Hamster Embryo Cells.** (Eng) MacLeod, M. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Cohen, G. M.; Selkirk, J. K. *Cancer Res* 39(9): 3463-3470; 1979.

The metabolism and macromolecular binding of benzo(a)pyrene (BP) and its relatively inert structural isomer benzo(e)pyrene (BEP) were studied to determine whether a metabolic basis exists for their different biological activities. BP was metabolized more extensively than BEP to both ethyl acetate-soluble and water-soluble metabolites. The major ethyl acetate-soluble metabolite in the medium after a 24-hr culture with BP was the bay region 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene (9,10-dihydrodiol: 66.7% of the total metabolites). Smaller amounts of 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene (7,8-dihydrodiol) were found, but more of this dihydrodiol than the 9,10-dihydrodiol was retained intracellularly, where it could be metabolized to an active diol-epoxide. The major metabolites found in the cytoplasm were 9-hydroxybenzo(a)pyrene and 3-hydroxybenzo(a)pyrene (40.7% and 16.5% of the metabolites, respectively) and the 7,8-dihydrodiol (18.4% of the metabolites). The 9,10-dihydrodiol formed 9.2% of the metabolites. The major ethyl acetate-soluble metabolite formed in the extracellular medium after a 24-hr culture with BEP was the K-region dihydrodiol 4,5-dihydro-4,5-dihydroxybenzo(e)pyrene (69.6% of the organic solvent-soluble metabolites); small amounts of monohydroxybenzo(e)pyrenes (21.9% of the organic solvent-soluble metabolites) were also formed. Most of the latter and significant amounts of the former were metabolized to their respective water-soluble glucuronide conjugates. The metabolic formation of 7,8-dihydrodiol from BP and the apparent lack of formation of 9,10-dihydro-9,10-dihydroxybenzo(e)pyrene from BEP suggests that there is a metabolic basis for the relative biological activities of the parent hydrocarbons. (34 refs)

- 79-6333 **The Formation of Dihydrodiols from Benzo(a)pyrene by Oxidation with an Ascorbic Acid/Ferrous Sulphate/EDTA System.** (Eng) Hewer, A. (Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, Lon-

don SW3 6JB, England); Ribeiro, O.; Walsh, C.; Grover, P. L.; Sims, P. *Chem Biol Interact* 26(2): 147-154; 1979.

Four dihydrodiols were produced by the oxidation of benzo(a)pyrene in an ascorbic acid/ferrous sulfate/EDTA system. trans-4,5-Dihydro-4,5-dihydroxybenzo(a)pyrene, trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and trans-9,10-dihydro-9,10-dihydroxybenzo(a)pyrene were identified by their UV spectra and by direct comparisons of their chromatographic properties, using high-pressure liquid chromatography, with those of the authentic compounds. The fourth compound appeared to be trans-11,12-dihydro-11,12-dihydroxybenzo(a)pyrene, since its UV spectrum was identical to that of the cis-dihydrodiol. Time-course experiments showed that the max amounts of products were obtained after 8 hr of oxidation. A reexamination of the dihydrodiols formed from benzo(a)pyrene by rat liver microsomal fractions failed to show the formation of the trans-11,12-dihydrodiol. (16 refs)

- 79-6334 Differences in Mutagenicity and Cytotoxicity of (+) and (-)-Benzo[a]pyrene 4,5-Oxide: A Synergistic Interaction of Enantiomers. (Eng) Chang, R. L. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110); Wood, A. W.; Levin, W.; Mah, H. D.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *Proc Natl Acad Sci USA* 76(9): 4280-4284; 1979.

The (+) and (-) enantiomers of benzo(a)pyrene (BP)-4,5-dioxide were compared with respect to their mutagenicity for four strains of *Salmonella typhimurium* and their mutagenicity and cytotoxicity for Chinese hamster V79 cells. A linear dose-response relationship was seen in all four bacterial strains. The (-) enantiomer was 1.5- to 5.5-fold more mutagenic than the (+) enantiomer for *S. typhimurium* strains TA98, TA100, TA1537, and TA1538 and for V79 cells. The (-) enantiomer was also more cytotoxic for V79 cells than was the (+) enantiomer. When mixtures of the enantiomers were studied using V79 cells, synergistic cytotoxic and mutagenic effects were observed. The greatest effects were observed using a 3:1 mixture of the (-) and (+) enantiomers. (28 refs)

- 79-6335 DNA-Benzo(a)pyrene Adducts Formed in a *Salmonella typhimurium* Mutagenesis Assay System. (Eng) Santella, R. M. (Div. Environmental Science, Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY); Grunberger, D.; Weinstein, I. B. *Mutat Res* 61(2): 181-189; 1979.

The DNA adducts formed in *Salmonella typhimurium* when the bacteria were incubated with radioactive benzo(a)pyrene (BP) and liver microsomal enzymes from different sources were studied. When enzyme preparations from Aroclor 1254- or 3-methylcholanthrene-induced C57BL/6N (B6) mice were used to mediate activation, the predominant product was an adduct between the 10 position of 7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydro-BP and the N-2 position of deoxyguanosine. Similar results were obtained with human liver and with Aroclor-induced rat liver enzyme preparations. This adduct was also the major DNA product found previously when human tissues or certain rodent cells were incubated with BP. When activation of BP was mediated by a phenobarbital-induced B6 mouse liver enzyme preparation, the extent of binding was quite low and the profile of DNA adducts in *S. typhimurium* DNA was quite different. Thus, under appropriate conditions, the activation and DNA binding of

BP in the microsome-mediated *S. typhimurium* assay generally resembles that seen in intact mammalian cells. Caution must be exercised, however, in the choice of microsome-activation systems. (21 refs)

- 79-6336 A Quantitative Comparison of the Mutagenicity of Carcinogenic Polycyclic Hydrocarbon Derivatives in Cultured Mammalian Cells. (Eng) Newbold, R. F. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Brookes, P.; Harvey, R. G. *Int J Cancer* 24(2): 203-209; 1979.

A series of reactive hydrocarbon derivatives was tested for cytotoxicity and ability to induce 8-azaguanine-resistant mutants in Chinese hamster V79/4-K₁ cells. The anti- and syn-benzo(a)pyrene-7,8-dihydrodiol-9,10-oxides (I and II, respectively), 1-oxiranylnaphthalene, and 7-bromomethylbenzo(a)anthracene (IV) were more effective mutagens than the other compounds tested. In V79 cells cocultured with a feeder layer of hydrocarbon-metabolized BHK 21/13 fibroblasts, anti-BP-diol epoxide (I) was the most potent mutagen (mutation frequency plotted as a function of percentage survival), particularly in its ability to induce large numbers of mutants at minimally lethal doses. II, IV, and BP-4,5-oxide were indistinguishable with respect to their mutagenicities. At equal extents of DNA reaction, IV, I, and syn-BP-diol epoxide were essentially equally cytotoxic, but I was four- to eightfold more mutagenic than the others at equal levels of binding. Thus, I had a higher "absolute mutagenic efficiency" (mutagenicity per unit extent of DNA reaction). (40 refs)

- 79-6337 Mutagenic Cholesterol Preparations. (Eng) Smith, L. L. (Div. Biochemistry, Dept. Human Biological Chemistry and Genetics, Univ. Texas Medical Branch, Galveston, TX 77550); Smart, V. B.; Ansari, G. A. *Mutat Res* 68(1): 23-30; 1979.

Naturally air-aged commercial samples of cholesterol stored for different lengths of time were tested for mutagenicity toward five *Salmonella typhimurium* strains. Dose-response mutagenicities were obtained without metabolic activation for five of six naturally air-aged samples tested at 1.2-12 mg/plate with strains TA1537, TA1538, and TA98 (frame-shift mutagens); they were not mutagenic with strains TA1535 and TA100 (base-pair mutagens). Pure crystalline cholesterol free from detectable autooxidation products was nonmutagenic in all five strains. Similar dose-response relationships were obtained with strains TA1537, TA1538, and TA98 over the sample range 1.2-12 mg/plate for pure non-mutagenic cholesterol after it had been heated to 70 C in air or γ -irradiated in air. Several individual cholesterol autooxidation products were tested with these same strains and were nonmutagenic at levels as high as 6 mg/plate. These results show that unidentified autooxidation products of cholesterol are frameshift mutagens in *Salmonella* and demonstrate that the sterols and unsaturated lipids are classes of important biological compounds from which mutagens may derive. (54 refs)

- 79-6338 Biosynthesis of Cholesteryl 14-Methylhexadecanoate in the Liver of Rats Bearing Transplantable Tumors and During Chemical Carcinogenesis. (Eng) Kvcála, J. (Oncological Inst., 180 00 Prague 8, Czechoslovakia); Hradec, J. *Neoplasma* 26(1): 29-38; 1979.

The biosynthesis of cholesteryl 14-methylhexadecanoate, cholesteryl palmitate, and cholesteryl stearate was studied in the liver of female Wistar rats bearing Walker 256 carcinomas and Zajdela hepatomas and during chemical carcinogenesis induced by benzo(a)pyrene. The production of all three esters was enhanced up to ninefold in liver homogenates during days 10-16 after transplantation of the Walker tumor. Only the enzyme system esterifying cholesterol in the cytosol at pH 6.5 was stimulated; the activity of similar enzymes in mitochondria, microsomes, and cytosol at an acid pH was not affected. The activity of the cytosol enzyme esterifying cholesterol at pH 6.5 was also enhanced during active growth of the Zajdela hepatoma and during chemical carcinogenesis characterized by the appearance of palpable sc tumors. The enhanced activity of the cholesterol-esterifying enzymes in the liver coincided with the periods of elevated cholesteryl 14-methylhexadecanoate levels in the liver and blood plasma as described earlier. An increased demand of the tumor-bearing host for this cholesteryl ester, which is utilized as a cofactor for enhanced protein synthesis, is met by its stimulated production in the liver tissue. (18 refs)

- 79-6339 The Relationship Between Zinc and Vitamin A in Cancer Patients. (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Williams, D. C. *IRCS Med Sci [Cancer]* 7(7): 361; 1979.

Serum zinc level and its possible correlation with vitamin A status were studied in 245 cancer patients and 22 age-matched controls. Serum levels of both zinc and vitamin A in the patients and controls were within normal limits, but the zinc levels were higher ($p < 0.05$) and the vitamin A levels lower ($p < 0.05$) in the patients than in the controls. Both vitamin A and zinc levels were significantly higher in the 77 breast cancer patients than in the other cancer patients. Excluding the values for the female breast cancer patients, there were no significant sex differences among the cancer patients. The data suggest that serum vitamin A level may be dependent on zinc when limited amounts of this metal are available. (9 refs)

- 79-6340 The Metabolic Activation of *trans*-4-Dimethylaminostilbene After Oral Administration of Doses Ranging from 0.025 to 250 $\mu\text{mol/kg}$. (Eng) Neumann, H. G. (Inst. Pharmacology and Toxicology, Univ. Wurzburg, Wurzburg, W. Germany); Gaugler, B. J.; Taupp, W. In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 177-190; 1978.

^3H -*trans*-4-dimethylaminostilbene (*trans*-DAS) was given po to female Wistar rats at one of five doses (0.025, 0.25, 2.5, 25, or 250 $\mu\text{moles/kg}$). The animals were sacrificed 5 hr later; and the total radioactivity bound to liver proteins and nucleic acids, plasma proteins, and Hb was determined. Total radioactivity increased linearly with dose in liver and blood at the three lower doses; but at the higher doses, the tissue radioactivity rose less proportionately. Three soluble liver protein fractions, liver DNA and RNA, and plasma proteins all demonstrated a biphasic correlation between metabolite binding and dose. At the three lower doses, the radioactivity increased in proportion to dose but was less than directly proportional after administration of the higher doses. These results demonstrate that *trans*-DAS metabolites, including those

that can react with cellular macromolecules, are distributed within the liver cell and into the circulation in a manner remarkably independent of the dose. It was concluded that the relative rates of the reactions encountered in the metabolism of this compound remain constant over a wide range of doses; the relative rates of the metabolic reactions may not have changed in the higher dose range, but rather the rate of absorption may have decreased. Since binding to such different macromolecules as proteins, RNA, and DNA depended on the dose in the same way, total binding may be a relative measure of the biochemical lesion induced by an individual dose of *trans*-DAS. (32 refs)

- 79-6341 Metabolites of Diethylstilboestrol Induce Sister Chromatid Exchange in Human Cultured Fibroblasts. (Eng) Rudiger, H. W. (Universitäts-Krankenhaus, Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany); Haenisch, F.; Metzler, M.; Oesch, F.; Glatt, H. R. *Nature* 281(5730): 392-394; 1979.

The induction of sister chromatid exchange (SCE) in cultured human fibroblasts, by diethylstilbestrol and two of its metabolites, diethylstilbestrol- α,β -oxide (DES- α,β -oxide) and β -dienestrol was investigated. In diploid fibroblast cultures from five different donors, lower concentrations of DES were sufficient to cause SCE than of the positive control, benzo(a)pyrene (BP). An increase in SCE was observed at even lower concentrations of DES- α,β -oxide and β -dienestrol than of DES. Concentrations required for half maximal induction of SCE by DES, DES- α,β -oxide, β -dienestrol, and BP were 133 nM, 40 nM, 5 nM, and 2,100 nM, respectively. The induction of SCE by DES was completely inhibited by α -naphthoflavone, a monooxygenase inhibitor, and was markedly inhibited by β -dienestrol. The SCE-induction obtained with DES- α,β -oxide was decreased by 35% in the presence of α -naphthoflavone. These results indicate that DES and also β -dienestrol require metabolic activation by monooxygenase for the induction of SCE. Neither DES nor its two metabolites induced mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98. (21 refs)

- 79-6342 Evaluation of the Transplacental Toxicity of Diethylstilbestrol with the Scanning Electron Microscope. (Eng) Lamb, J. C. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Newbold, R. R.; McLachlan, J. A. *J Toxicol Environ Health* 5(4): 599-603; 1979.

Exposure in utero to the synthetic estrogen diethylstilbestrol (DES) is associated with reproductive tract lesions in male and female CD-1 mice. The scanning electron microscope was used to evaluate the luminal surface of the vagina, cervix, and uterus of these mice following prenatal exposure to DES (10 $\mu\text{g/kg}$ sc on gestation days 9-16). Observed abnormalities included urethral openings in the cervicovaginal area, squamous metaplasia of the uterus, glandular elements in the vagina, and abnormal cell-surface features in the vaginal epithelium. (8 refs)

- 79-6343 Risks of Chemical Pollution of Drinking Water. I. Study of Long-Term Toxicity of Chloroform-extractable Organic Micropollutants from Drinking Water Used for Human Consumption in Rats and Mice. (Fre) Truhaut, R. (Centre de Recherches Toxicologiques, Faculte des Sciences, Phar-

maceutiques et Biologiques de Paris-Luxembourg, 4, avenue de l'Observatoire, 75006 Paris, France); Gak, J. C.; Graillot, C. *Water Res* 13(8): 689-697; 1979.

The effects of organic pollutants extracted with chloroform at pH 7 from drinking water in Paris were tested in 50 rats and 50 mice of both sexes. The animals received a diet containing 100 or 200 times more organic pollutant than would be consumed by a 60-kg human drinking 3 liters of water daily; the diet was administered from the time of weaning until death. The incidence of malignant tumors was 0% in control male rats, 33.3% in males treated with the 100x dose, and 50% in males treated with the 200x dose. In female rats, the incidence of malignant tumors was 4.5% in the controls, 40% in the 100x dose group, and 57.1% in the 200x dose group, ie, there was a dose-response relationship in both male and female rats. In the mice, the incidence of malignant tumors was 4.9% in male controls and 11.1% in males treated with 100x and 200x doses. Malignant tumors were found in 14.3% of control female mice, in 43.8% of females given the 100x dose, and in 45% of those given the 200x dose; thus, significant increases in tumor incidence were found in female mice only, but there was no dose-response relationship in either sex. The tumors were mainly mammary and ovarian adenocarcinomas in female rats, thyroid tumors in male rats, and lymphosarcomas in both sexes; all three tumors were also found in mice. (18 refs)

- 79-6344 Risks of Chemical Pollution of Drinking Water. II. Comparative Studies on the Long-Term Toxicity of Organic Micropollutants Extracted from Waters Used in Drinking Water Preparation. (Fre) Graillot, C. (Centre de Recherches Toxicologiques, Faculte des Sciences Pharmaceutiques et Biologiques de Paris-Luxembourg, 4, avenue de l'Observatoire, 75006 Paris, France); Gak, J. C.; Lancret, C.; Truhaut, R. *Water Res* 13(8): 699-710; 1979.

Fifty rats and 60 mice (half males and half females) received, from the time of weaning, a diet containing chloroform-extracted organic pollutants from raw river water used for drinking water preparation. The extracts were divided into fractions with low (f) and high (F) cytotoxicity, established by preliminary cytotoxicity tests. Each fraction was tested in doses of 25 mg/kg (f1 and F1) and 50 mg/kg (f2 and F2). In male mice, the incidence of malignant tumors was 0% in the controls, 5.9% in group f1, 5.3% in f2, 0% in F1, and 10.5% in F2. In female mice, the tumor incidence was 8% in the controls, 59.3% in f1, 52.4% in f2, 59.3% in F1, and 59.1% in F2. In male rats, the tumor incidence was 9.1% in the controls, 17.7% in f1, 47.4% in f2, 11.8% in F1, and 36.8% in F2. In female rats, the tumor frequency was 4.8% in the controls, 9.5% in f1, 36.4% in f2, 16.7% in F1, and 42.9% in F2. Although there was a dose-response relationship, there was no correlation between the degree of cytotoxicity and the incidence of malignant tumors. The tumors were mainly adenocarcinomas of the mammary gland, lymphosarcomas, and other sarcomas. (9 refs)

- 79-6345 Effects of Progesterone on Mammary Carcinogenesis by DMBA Applied Directly to Rat Mammas. (Eng) Jabara, A. G. (Dept. Veterinary Paraclinical Sciences, Univ. Melbourne, Parkville, Victoria 3052, Australia); Marks, G. N.; Summers, J. E.; Anderson, P. S. *Br J Cancer* 40(2): 268-273; 1979.

The effects and site(s) of action of progesterone (3 mg/day, 3x/wk, sc) on 7,12-dimethylbenz(a)anthracene (DMBA)-induced

mammary carcinogenesis were studied in the female Sprague-Dawley rat. The surgically exposed right fourth mammary gland was dusted with 2 mg of powder containing a DMBA-cholesterol mixture (1:1). Tumors developed only in DMBA-treated mammary glands. In animals treated with progesterone for 135 or 197 days, 29/51 that developed mammary carcinomas also developed nonmammary neoplasms of the skin or body wall at the site of DMBA dusting. The mammary tumor incidence and av tumor latent period was similar in rats treated with DMBA alone and those treated with progesterone for 18 days prior to DMBA treatment. However, in rats treated with progesterone starting 2 days before and continuing for 135 days after DMBA treatment, the tumor incidence was greater and the latent period shorter than in the DMBA-only group ($P < 0.05$). In general, progesterone treatment before DMBA treatment had no influence on mammary tumorigenesis, whereas progesterone treatment after DMBA treatment stimulated continuous tumor growth ($P < 0.01$). Tumor size was also greater in rats treated with progesterone after DMBA; at autopsy, 53% of the neoplasms in these animals had obtained an av size of ≥ 2 cm, compared with only 89% and 25% in groups treated with progesterone before DMBA administration. All mammary carcinomas were adenocarcinomas, and progesterone did not influence their macro- or microscopic appearance. Most nonmammary neoplasms were fibrosarcomas. The data suggest that progesterone may exert its inhibitory effect on carcinogenesis via action at a site outside the breast, perhaps the liver. However, it is likely that the hormone acts directly on the mammary tissue to enhance tumorigenesis. (18 refs)

- 79-6346 Steroid Binding Proteins of Mammary Tissues and Their Clinical Significance in Breast Cancer. (Eng) Wittliff, J. L. (Dept. Biochemistry, Univ. Louisville Sch. Medicine, Louisville, KY 40232); Lewko, W. M.; Park, D. C.; Kute, T. E.; Baker, D. T.; Kane, L. N. *Prog Cancer Res Ther* 10: 325-359; 1978.

Data regarding the kinetic and molecular characteristics of steroid binding proteins in normal mammary gland and in several hormonally responsive rat mammary tumors and human breast tumors are summarized. In general, the kinetic and molecular properties of estrogen receptors (EGR's), glucocorticoid R's, and progesterin R's in normal rat mammary tissues and tumors were similar. These R's were studied in hormonally responsive mammary tumors induced in female rats by N-nitrosomethylurea and 7,12-dimethylbenz(a)anthracene, those induced in female C3H mice by EG's, and the hormonally responsive R3230AC mammary tumor, which is transplantable in female Fischer 344 rats. Studies of the influence of EGR complexes on RNA polymerase activity suggest that the activation of mammary gland estradiol-R complexes is a prerequisite for its nuclear translocation and subsequent stimulation of nuclear synthetic activity. The distributions of both the EG and progesterone R's in a breast tumor may be predictive indices of a response to hormone manipulation. In general, the specific EG binding capacities of mastectomy specimens of patients with no nodal involvement were similar to those of patients with nodal involvement. The 8S EGR of lactating mammary gland was composed of at least two components, each with different ionic properties. The 8S EGR of human breast tumors separated into a variable number of components with different ionic properties, and the 4S EGR of these tumors separated into at least two components with different ionic properties. The data suggest that EGR's of human breast cancers exhibit molecular heterogeneity and that the molecular properties of EGR's in human breast tumor biopsies may be related to the clinical responsiveness of patients treated by hormonal manipulations. (47 refs)

79-6347 Progesterone and Estrogen Receptors in Japanese Breast Cancer. (Eng) Matsumoto, K. (Inst. Cancer Res., Osaka Univ. Medical Sch., Kita-ku, Osaka 530, Japan); Ochi, H.; Nomura, Y.; Takatani, O.; Izuo, M.; Okamoto, R.; Sugano, H. *Prog Cancer Res Ther* 10: 43-58; 1978.

The presence of estrogen receptors (ER) and progesterone receptors (PR) among 1,060 Japanese breast cancer patients was studied. Measurable numbers of ER were found in 615/1,060 (58%) of the cancers studied. This rate is within the lowest range of rates reported in Western countries. The rates of ER-positive tumors among pre- and postmenopausal Japanese women were similar to those among Western women. Forty-one of 82 ER-positive breast cancers responded to endocrine therapy, as compared with only 5/57 ER-negative cancers. The response rates were similar to those in Western patients. Measurable numbers of PR were found in 171/474 Japanese breast cancers. This rate is somewhat lower than that observed among Western patients. PR was found in 51% of ER-positive cancers and 13% of ER-negative cancers. The frequency of PR increased with ER content. Positive responses to endocrine therapy were obtained with 12/20 tumors positive for ER and PR, 9/25 tumors positive for ER but not PR, 2/20 tumors negative for ER and PR, and 0/1 positive for PR but not ER. The data indicate that assays of ER and/or PR are useful for predicting the response to endocrine therapy for breast cancer among patients of any race. (35 refs)

79-6348 Prevention and Treatment of Endometrial Disease in Climacteric Women Receiving Oestrogen Therapy. (Eng) Thom, M. H. (King's Coll. Hosp., London, England); White, P. J.; Williams, R. M.; Sturdee, D. W.; Paterson, M. E.; Wade-Evans, T.; Studd, J. W. *Lancet* 2(8140): 455-457; 1979.

The treatment regimens in 74 women with endometrial disease among 850 climacteric women receiving estrogen or estrogen-progestagen therapy were studied. Cystic hyperplasia was associated with unopposed estrogen therapy without progestagen. Two 21-day courses of treatment with norethisterone (5 mg/day) caused reversion to normal in all 57 cases of cystic hyperplasia and in 6/8 cases of adenomatous hyperplasia, but had no such effect in two cases of atypical hyperplasia. Four cases of endometrial carcinoma demonstrated the problems associated with inappropriate and unsupervised unopposed estrogen therapy and the difficulty in distinguishing between severe hyperplasia and malignancy. Cyclical low-dose estrogen therapy combined with 7-13 days of progestagen therapy did not appear to increase the risk of endometrial hyperplasia or carcinoma. (19 refs)

79-6349 Hormone Receptors and Histopathology in Japanese Breast Cancer. (Eng) Sugano, H. (Dept. Pathology, Cancer Inst., Japanese Foundation Cancer Res., Toshima-ku, Tokyo 170, Japan); Sakamoto, G.; Sakamoto, A.; Nomura, Y.; Takatani, O.; Matsumoto, K. *Prog Cancer Res Ther* 10: 59-70; 1978.

Relationships between histopathological types of breast cancer and estrogen, progesterone, and androgen receptors (ER, PR, and AR) were studied among Japanese women, and the results were compared with those obtained among American women. Except for a low incidence of lobular carcinoma among Japanese women, the distributions of histological types of breast cancer among Japanese and American women did not differ greatly. Of the Japanese cancers analyzed, 188/324 were positive for ER, 59/179 were

positive for PR, and 21/80 were positive for AR. ER were present in a high percentage of lobular carcinomas, and the frequencies of ER, PR, and AR were low in cancers showing lymphocyte infiltration. These tendencies, which were not statistically significant, were similar to those observed in American cancers. A significantly low frequency of PR and ER/PR, and a nonsignificantly low frequency of ER were observed in medullary tubular carcinomas. There was no remarkable relationship between histological factors of prognostic significance and the presence of hormone receptors, but the ER distribution tended to parallel that of PR. The hypothesis that local lymphocyte infiltration is related to a good prognosis for breast cancer among the Japanese was not supported. (33 refs)

79-6350 Effect of Contraceptive Steroids on Mammary Gland of Beagle Dog and Its Relevance to Human Carcinogenicity. (Eng) El Etreby, M. F. (Dept. Experimental Toxicology and Endocrine Pharmacology, Res. Labs. Schering AG, Berlin Bergkamen, 1000 Berlin 65, W. Germany); Graf, K. J. *Pharmacol Ther* 5(1-3): 369-402; 1979.

The effects of various progestagens, estrogens, and progestagen-estrogen combinations on the dog mammary gland were studied, and the results were discussed together with those of previous systemic tolerance tests and carcinogenicity studies. Mammary gland hyperplasia occurred in a dose-dependent fashion after treatment with progesterone, progestagens, estrogens, and hormone combinations. These hyperplastic processes occurred from the fourth wk of treatment onward and could be reversed in spite of continued treatment. Estrogens seemed to induce predominantly proliferation and ectasia of the ductal system of the canine mammary glands, with no signs of alveolar development. Progestagens mainly caused dose-dependent lobulo-alveolar growth, including epithelial and myoepithelial proliferation. This effect was evident for certain progestagens even in doses below or nearly at the minimal human ovulation-suppressing dose. In several long-term studies with progesterone and certain progestagens and progestagen-estrogen combinations, an increased number of mammary nodules was observed from the second or third yr onward, even with doses as low as the human ovulation-suppressing dose. 0 Ethinyl estradiol, mestranol, and some 19-nortestosterone derivatives and their combinations did not significantly influence the occurrence of mammary nodules. The nodules could be reversed when treatment was continued or stopped. Most of the nodules were regarded as lobular hyperplasias or benign tumors, but some malignant tumors were also diagnosed. It is unlikely that steroid-related canine mammary tumors are indicative of a potential hazard to humans. (92 refs)

79-6351 Hormonally Induced Tumors of the Reproductive System of Parabiosed Male Rats. (Eng) Brown, C. E. (Cancer Res. Inst., New England Deaconess Hosp., 185 Pilgrim Road, Boston, MA 02215); Warren, S.; Chute, R. N.; Ryan, K. J.; Todd, R. B. *Cancer Res* 39(10): 3971-3976; 1979.

The appearance of neoplasms in the target organs of male rats parabiosed to castrated males or to oophorectomized females was studied. Among 20 parabiosed pairs completing the long-term experiment (387-750 days postcastration), 11 interstitial cell tumors of the testis and 4 adenocarcinomas of the prostate developed in the target partners. Eight of these tumors occurred in pairs in which each partner was unilaterally nephrectomized. Serum luteinizing hormone, follicle-stimulating hormone, testosterone, and androstenedione levels were elevated in the parabiosed pairs. The nonneoplastic testes of target partners showed slight increases in

weight over controls, and the prostates and seminal vesicles of the target partners were moderately enlarged and filled with thick, milky fluid. Microscopic foci of adenocarcinoma were found in the dorsolateral lobes of the prostates of four unilaterally nephrectomized target males. Many of the prostates of target partners showed apparent generalized hyperplasia. The data suggest that a correlation exists between internally generated gonadotropins and the development of interstitial cell tumors of the testis, and that there is a correlation between serum androgen levels and the development of prostate adenocarcinomas in rats. (18 refs)

- 79-6352 Contraceptive Hormones: The Problem of the Induction of Mammary Gland Nodules in Beagle Dogs Given Progestogens. (Eng) Graf, K. J. (Free Univ., Berlin, W. Germany); El Etreby, M. F.; Neumann, F. In: *Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977*. Plaa, G. L.; Duncan, W. A., eds. (New York: Academic Press, Inc.): 670 pp.; 225-243; 1978.

The role of chemical configuration, of progestogenic activity, and of the interference of progestogens with prolactin and/or growth hormone secretion is discussed in relation to the tumorigenicity of some progestogens in the canine mammary gland. Hydroxyprogesterone derivatives and 19-nor-testosterone derivatives as well as estrogens and estrogen-progestogen combinations induce proliferative mammary lesions in the dog. Previous studies were extended through the use of a progestogen test model using ovariectomized female beagles to estimate the transforming potency of progestogens at the canine endometrium. It was found that the 17 α -hydroxy-progesterone derivatives were much more powerful than the 19-nor-testosterone derivatives. In contrast, the 19-nor-testosterone derivatives are more active with respect to endometrial transformation in women. In the dog, progestogens and possibly growth hormone seem to be the main factors affecting mammary gland growth; however, in other species, the role of

estrogens remains to be clarified, and prolactin is assumed to be primarily responsible for functional secretory activity only. In a study of the influence of synthetic progestogens (cyproterone acetate, 100 mg/kg) on prolactin secretion, no significant differences were detected between the pre- and post-treatment prolactin concentrations. Histological examination of the mammary gland tissue, however, revealed proliferation of the duct system with signs of hyperplasia. It is concluded that the induction of mammary gland nodules in dogs by certain progestogens must be considered a species-specific effect. (25 refs)

See also:

- *(Rev.): 79-6002, 79-6003, 79-6004, 79-6005, 79-6006, 79-6007, 79-6008, 79-6009, 79-6010, 79-6011, 79-6012, 79-6013, 79-6014, 79-6015, 79-6016, 79-6017, 79-6018, 79-6019, 79-6020, 79-6021, 79-6022, 79-6023, 79-6024, 79-6025, 79-6026, 79-6027, 79-6028, 79-6029, 79-6030, 79-6031, 79-6032, 79-6033, 79-6034, 79-6035, 79-6036, 79-6037, 79-6038, 79-6039, 79-6040, 79-6041, 79-6042, 79-6043, 79-6044, 79-6045, 79-6046, 79-6047, 79-6048, 79-6049, 79-6050, 79-6051, 79-6052, 79-6053, 79-6054, 79-6055, 79-6056, 79-6057, 79-6058, 79-6059, 79-6060, 79-6061, 79-6062, 79-6063, 79-6064, 79-6065, 79-6066, 79-6067, 79-6071, 79-6081, 79-6097, 79-6098, 79-6102, 79-6104, 79-6105, 79-6106, 79-6107, 79-6108, 79-6109, 79-6110, 79-6111, 79-6112, 79-6113, 79-6115, 79-6116, 79-6126.
*(Phys.): 79-6358, 79-6359, 79-6361, 79-6363, 79-6365.
*(Viral): 79-6395, 79-6432, 79-6446.
*(Immun.): 79-6466, 79-6492, 79-6499, 79-6502, 79-6508, 79-6516.
*(Path.): 79-6531, 79-6550.
*(Epid.-Biom.): 79-6560, 79-6564, 79-6565, 79-6568, 79-6574, 79-6575, 79-6577, 79-6580, 79-6581, 79-6583, 79-6584, 79-6585, 79-6586.

PHYSICAL CARCINOGENESIS

- 79-6353 The Effects of β -Radiation on Sister-Chromatid Exchanges in Cultured Human Lymphocytes. (Eng) Crossen, P. E. (Cancer Society New Zealand, Cytogenetics Unit, Christchurch Hosp., Christchurch, New Zealand); Morgan, W. F. *Mutat Res* 62(1): 125-129; 1979.

The 5-bromodeoxyuridine/Giemsa technique was used to investigate the incidence of sister-chromatid exchanges (SCE's) due to β -radiation in cultured human lymphocytes. Cultures treated continuously with 0.001 or 0.01 μ Ci of [3 H]uridine for 48 hr showed no increase in either chromosome abnormalities or SCE's. Continuous treatment with 0.1 μ Ci resulted in a significant increase in chromosome aberrations but no increase in SCE's, whereas treatment with 0.2 μ Ci increased both chromosome aberrations and SCE's. Cultures given a 4-hr pulse with 1.0 μ Ci showed a significant increase in both SCE's and chromosome aberrations. The results indicate that low levels of β -radiation do not increase the incidence of SCE's in human lymphocytes and that several, if not all, the exchanges observed at low levels of β -radiation by autoradiography may be spontaneous events. (17 refs)

- 79-6354 Effects of UV-Light on DNA Synthesis in Photodermatoses. (Eng) Horkay, I. (Dept. Dermatology, Univ. Medical Sch. Debrecen, Debrecen 4012, Hungary); Varga, L.; Tamasi, P.; Gundy, S.; Nagy, E. *Fortschr Onkol* 4: 151-156; 1979.

The repair of UV-induced DNA damage and changes in semiconservative DNA synthesis in the epidermis were studied in eight patients with polymorphic light eruption (PLE), seven patients with porphyria cutanea tarda and erythropoietic protoporphyria (CP), one patient with xeroderma pigmentosum (XP), and six controls without photosensitivity. The percentage of cells showing semiconservative DNA synthesis (indicated by nuclei heavily labeled with thymidine) in the unirradiated, symptom-free skin of patients with photodermatosis did not differ significantly from that in the controls. A slight depression in the percentage of heavily labeled nuclei was observed in specimens of skin irradiated 2 hr previously with three times the minimal erythema dose (MED) of UV light. On skin irradiated daily with five times the MED, the original symptoms of the PLE patients were reproduced, and an erythematous sunburn reaction was observed in both CP patients and controls. The number of heavily labeled cells from such sites was greater than that from unirradiated sites. The av percentage of sparsely labeled epidermal nuclei (indicative of repair DNA synthesis) 2 hr after UV-irradiation with three times the MED did not differ between PLE and CP patients. The av grain-count per cell in PLE was similar to that in controls but was significantly lower in CP and especially lower in XP. Forty-eight hours after irradiation, no repair synthesis was detected in any of the biopsy specimens. The data suggest that some alterations in semiconservative and repair DNA synthesis are present in the epidermis of patients with photodermatosis. (14 refs)

- 79-6355 A Seventh Complementation Group in Excision-deficient Xeroderma Pigmentosum. (Eng) Keijzer, W.

(Dept. Cell Biology and Genetics, Erasmus Univ., P.O. Box 1738, Rotterdam, Netherlands); Jaspers, N. G.; Abrahams, P. J.; Taylor, A. M.; Arlett, C. F.; Zelle, B.; Takebe, H.; Kinmont, P. D.; Bootsma, D. *Mutat Res* 62(1): 183-190; 1979.

DNA excision repair by the cells of a xeroderma pigmentosum patient (XP2BI) was studied. XP2BI cells were sensitive to UV light, compared with cells from an unaffected individual. In a host cell-activation experiment using UV-irradiated simian virus 40 (SV40) circular DNA, the survival fraction of SV40 in XP2BI cells was lower than that in control cells. The UV-stimulated unscheduled DNA synthesis (UDS) pattern of XP2BI cells was characteristic for an excision-deficient XP strain. XP2BI cells did not show detectable excision of endonuclease-susceptible sites. The mol wts of the DNA from XP2BI cells were lower than those of control cells and higher than those of XP variant cells following UV exposure. This response was also characteristic for excision-deficient XP cells. When XP2BI cells were fused with cells from complementation groups A, B, C, D, E, and F, binuclear cells showing UDS levels in the range of normal cells were obtained. Thus, the XP2BI strain represents a new complementation group (group G). (13 refs)

- 79-6356 Enhanced Transformation of Xeroderma Pigmentosum Variant Cells by Ultraviolet Light-irradiated Simian Virus 40. (Eng) Hall, J. D. (Dept. Cellular and Developmental Biology, Univ. Arizona, Tucson, AZ 85721); Tokuno, S. *Cancer Res* 39(10): 4064-4068; 1979.

The role of DNA repair in transformation was investigated by infecting repair-deficient xeroderma pigmentosum (XP) variant cells, XP variant heterozygous cells, and normal human fibroblasts with UV-irradiated simian virus 40. The transformation frequencies obtained were compared with those observed for nonirradiated virus. Although the transformation frequencies of normal fibroblasts and heterozygous XP variant cells infected with irradiated virus were similar to those of normal and heterozygous cells infected with untreated virus, two XP variant cell lines were transformed two- to sevenfold more readily with irradiated virus than with nonirradiated virus. XP variant cells also produced lower than normal quantities of virus following infection with either damaged or undamaged virus, suggesting that increased viral production was not contributing to the increased transformation seen for these cells. The proportion of cells that repaired UV-irradiated simian virus 40 was similar for wild-type and XP variant cells, suggesting that enhanced transformation in the mutant cells was not associated with a reduction in the numbers of cells that repaired damaged virus. (25 refs)

- 79-6357 Defective Recovery of Semi-conservative DNA Synthesis in Xeroderma Pigmentosum Cells Following Split-Dose Ultraviolet Irradiation. (Eng) Moustacchi, E. (Institut Curie, Biologie, Centre Universitaire, Batiment 110, Orsay 91405, France); Ehmann, U. K.; Friedberg, E. C. *Mutat Res* 62(1): 159-171; 1979.

The effects of split- vs single-dose exposures to UV radiation on the recovery of DNA synthesis by two different normal diploid fibroblast strains (GM38 and GM316), xeroderma pigmentosum (XP) cells, and an XP variant (XPV) were compared. After a single-dose exposure, there was a dose-dependent decrease in DNA synthesis in the normal cells for 3-4 hr and then a dose-dependent increase in DNA synthesis after 4-6 hr. The max inhibition of DNA synthesis and delay in recovery were reduced after split-dose exposure, compared with single-dose exposure, and the max level of DNA synthesis was higher. Similar results were obtained with symmetrical and asymmetrical split doses. Caffeine did not produce a synergistic effect with UV radiation after single- or split-dose exposures. XPV cells showed no enhancement in recovery of DNA synthesis after split-dose compared with single-dose irradiation, and caffeine had no effect on the overall pattern of kinetics. Dose fractionation also did not alter the recovery of DNA synthesis in XP cells of complementation groups A and C; similar results were obtained with XP cells of complementation group D. (43 refs)

79-6358 A Study of the Effect of Caffeine upon Excision Repair of Damaged DNA. (Eng) Apfelzweig, R. A. (Div. Cytogenetics and Cytology, City Hope Natl. Medical Center, 1500 E. Duarte Road, Duarte, CA 91010); Teplitz, R. L. *Mutat Res* 62(1): 151-158; 1979.

The effect of caffeine on the excision repair of damaged DNA was studied in peripheral blood lymphocytes from healthy donors. The lymphocytes were treated with UV light or 4-nitroquinoline 1-oxide (4NQO) to produce pyrimidine dimers or adducts, and caffeine (0.75-3.0 mM) was added to some cultures. Lymphocytes from patients with systemic lupus erythematosus (SLE) who had previously demonstrated reduced levels of excision repair under these conditions were also tested. Caffeine did not inhibit repair by normal lymphocytes, and it did not further reduce the reduced repair seen in the cells of the SLE patients. In a series of pulse-chase experiments, some cells were treated with 4NQO and incubated with ³H-thymidine for 3 hr before harvesting; others were given a 13-hr chase in cold thymidine before harvest. The counts per minute per microgram of DNA for both groups were virtually identical, both in the presence and absence of 2.0 mM caffeine. It is concluded that, although single-stranded DNA is available to caffeine during excision repair, DNA polymerase binds with greater affinity and repair continues at an expected rate. (22 refs)

79-6359 Sister Chromatid Exchanges in Lymphocytes Treated with 8-Methoxypsoralen and Exposed to Long-Wave Ultraviolet Light. (Eng) Faed, M. (Cytogenetics Lab., Dept. Pathology, Ninewells Hosp. and Medical Sch., Dundee DD2 1UB, Scotland); Mourelatos, D. In: *Mutagen-induced Chromosome Damage in Man. Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977*. Medical Research Council (Edinburgh, Scotland): 355 pp.; 52-61; 1978.

Human lymphocytes were obtained from eight psoriasis patients prior to treatment, 11 patients undergoing photochemotherapy with 8-methoxypsoralen (8-MOP) and long-wave UV light (UVA), and 13 healthy adults in order to investigate the effect of this treatment on the induction of sister chromatid exchanges (SCE's). The drug was added to blood from normal donors and, when appropriate, irradiation by UVA followed 30 min later. Samples were collected from treated patients 2 hr after oral ingestion of 8-MOP but before UVA irradiation and again 30 min later following

irradiation. Up to a concentration of 4 µg/ml, 8-MOP alone had no measurable effect on SCE's; but with both 8-MOP and UVA, there was an increase in SCE level related to the dose of 8-MOP. Patients who had not received treatment had SCE levels similar to those of the normal subjects. Treated patients had a marginally higher mean SCE rate (not statistically significant). In vitro irradiation of the blood increased the mean SCE rate to a level that was estimated to indicate a circulating 8-MOP concentration of approx 0.8 µg/ml. The SCE distribution became bimodal as 8-MOP concentration increased, with a significant proportion of the population of cells showing little or no increase in SCE rate. The significance of these observations are discussed, and it is concluded that 8-MOP/UVA therapy appears to have no effect on SCE's in the lymphocytes of psoriasis patients. (9 refs)

79-6360 Neoplastic Transformation and Dose Fractionation: Does Repair of Damage Play a Role? (Eng) Elkind, M. M. (Mammalian Cell Biology Group, Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439); Han, A. *Radiat Res* 79(2): 233-240; 1979.

The induction of neoplastically transformed cells after single and fractionated doses of 50 kV x-rays and fission-spectrum neutrons was measured. Combining the results with those of parallel measurements of cell survival permitted analysis of the possible roles of repair processes in the expression of sublethal and subtransformation damage. It is concluded that subtransformation damage due to x-rays is repaired, although probably more slowly than sublethal x-ray damage. Much less, if any, repair occurs between neutron doses during periods up to 24 hr. It is also concluded that repair of damage does play a role in neoplastic transformation when doses of a sparsely ionizing radiation are fractionated. (12 refs)

79-6361 DNA Repair and Malignant Transformation: Effect of X Irradiation, 12-O-Tetradecanoyl-phorbol-13-acetate, and Protease Inhibitors on Transformation and Sister-Chromatid Exchanges in Mouse 10T1/2 Cells. (Eng) Little, J. B. (Lab. Radiobiology, Dept. Physiology, Harvard Univ., Sch. Public Health, Boston, MA 02115); Nagasawa, H.; Kennedy, A. R. *Radiat Res* 79(2): 241-255; 1979.

The changes which occur in survival and the frequencies of chromosomal aberrations, sister-chromatid exchanges (SCEs), and malignant transformation during recovery from potentially lethal x-ray damage (PLD) in density-inhibited mouse 10T1/2 cells were measured. During the first 4 hr after irradiation, there was a parallel increase in survival, transformation, and SCEs, but a decrease in aberrations. With recovery intervals of 4 to 12 hr, there was no further change in survival or aberrations, but both transformation and SCEs declined markedly. Transformation induced by x-rays alone or combined with application of the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), was suppressed by exposure to the protease inhibitor antipain. In PLD-recovery experiments, TPA was found to enhance both spontaneous and direct x-ray-induced (no recovery) SCEs, but to have no effect on recovery-induced SCEs. Two hypotheses are proposed to explain the results: there may be two biologically important classes of DNA lesions and repair processes induced by x-irradiation, one primarily responsible for cell killing and one which leads primarily to mutations and transformation; and mitotic recombination reflected by SCEs is an important step in the expression of radiation damage in terms of transformation, as

it allows segregation of x-ray-induced recessive mutations in daughter cell populations. (39 refs)

- 79-6362 Premature Chromosome Condensation Following X Irradiation of Mammalian Cells: Expression Time and Dose-Response. (Eng) Griffiths, T. D. (Dept. Radiation Biology and Biophysics, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY 14642); Carpenter, J. G. *Radiat Res* 79(1): 187-202; 1979.

The expression time of premature chromosome condensation (PCC) in Chinese hamster ovary (CHO) cells exposed to 300-kilovolt peak x-rays was investigated in terms of cell-cycle position at the time of exposure. PCC was first detected in the mitosis that followed the second postirradiation (P1) S phase. Thus, cells irradiated in G1 first expressed PCC at the second P1 mitosis, but cells irradiated in G2 did not express PCC until the third P1 mitosis. Cells irradiated in the S phase expressed PCC at the second P1 mitosis with a frequency that was related to the position of the cells in the S phase at the time of exposure, with cells in the first half of the S phase (at the time of exposure) showing a higher frequency than cells positioned in the second half. Thus, DNA replication during the first P1 S phase may be involved in the processing of lesions that eventually give rise to PCC. For cells in G1 at the time of exposure, the D_0 for PCC expression at the second P1 mitosis was around 825 rads, indicating that PCC may play only a minor role in x-ray-induced cell killing. Autoradiographic analysis indicated that approx 50% of the PCC patches scored were replicating DNA at the time condensation was attempted. Daughter cells derived from these cells would suffer loss of genetic material. (44 refs)

- 79-6363 Immunity to Carcinogen-induced Transplantable Fibrosarcomas in B2/B2 Chickens. IV. Effect of Whole-Body Gamma Radiation on Localization and Growth of Intravenously Injected Tumor Cells. (Eng) Palladino, M. A. (Sloan Kettering Inst. Cancer Res., New York, NY); Galton, J. E.; Hochwald, G. M.; Thorbecke, G. J. *J Natl Cancer Inst* 63(3): 737-743; 1979.

Growth of a chemically induced transplantable fibrosarcoma (SCFSI) was observed 2 wk after iv injection of 2×10^7 tumor cells into histocompatible B2/B2 (SC) chickens. About 30% of recipients had tumor nodules in the stomach mucosa and pancreas, 10% in the lungs, and <10% in the heart. No relationship was seen between initial localization of ^{51}Cr -labeled SCFSI cells and sites of subsequent tumor growth: labeled cells localized primarily in liver (50%) and lung (24%). Total-body irradiation with gamma rays greatly enhanced tumor growth in stomach, pancreas, kidney, heart, lung, skeletal muscles, and liver but not in spleen, thymus, bursa, or brain. A single injection of *Corynebacterium parvum* either 1 wk before (-7) or on the day (0) of tumor inoculation did not affect the incidence of tumor growth (75%), whereas two injections of *C. parvum* on both days -7 and 0 completely prevented growth in the irradiated chickens. One-wk-old recipients showed as much tumor growth with or without irradiation, which suggested that the effect of irradiation in older recipients was partly due to damage of the immune response. The iv injection of 50 and 100 mg soybean trypsin inhibitor, 24 and 2 hr, respectively, prior to irradiation (450 rads) did not prevent the increased tumor growth caused by irradiation alone. Tumor cells from two additional SCFS lines (II and IV) also grew in the stomach and pancreas, but SCFSII was never found in heart or skeletal muscle, even in irradiated chickens. (44 refs)

- 79-6364 Failure of Irradiated Beef and Ham to Induce Genetic Aberrations in *Drosophila*. (Eng) Mittler, S. (Dept. Biological Sciences, Northern Illinois Univ., DeKalb, IL 60115). *Int J Radiat Biol* 35(6): 583-588; 1979.

Ham that had been irradiated by electrons [3.7-4.2 megarads (Mrad)] and beef that had been exposed to γ -rays from ^{60}Co (4.7-7.1 Mrad) were fed to *Drosophila melanogaster* males to determine whether meat sterilized by these methods would induce genetic aberrations. The entire spectrum of spermatogenesis was sampled by the brooding technique. yB/sc^yY males that had fed on electron-irradiated ham, ^{60}Co -irradiated beef, thermally preserved beef, or frozen beef showed no significant increase in the loss of X or Y chromosomes or in the nondisjunction of these chromosomes. There was no significant increase in any of the broods. Oregon R males that had spent their entire larval life on irradiated ham or beef, thermally preserved beef, or frozen beef also showed no significant increase in sex-linked recessive lethals. (11 refs)

- 79-6365 The Intercellular Distribution of Mutations Induced in Oocytes of *Drosophila Melanogaster* by Chemical and Physical Mutagens. (Eng) Traut, H. (Institut für Strahlenbiologie, Universität Münster, 4400 Münster, W. Germany). *Genetics* 92(1): 151-160; 1979.

The intercellular distribution of chemically and physically induced mutations in oocytes of *Drosophila melanogaster* was studied. In oocytes from females fed 5-fluorodeoxyuridine (12.5, 50.0, and 81.0 $\mu\text{g}/\text{ml}$), the frequency of mutations (mean, 0.13%) was not increased significantly above the spontaneous rate. There appeared to be little or no difference in the sensitivity of the two X chromosomes to the induction of mitomycin C (MMC: 130.0 $\mu\text{g}/\text{ml}$, po). The results were in accordance with the assumption of a random intercellular distribution of MMC-induced mutations in the oocytes of this species. The data also support the assumption that the mutations induced by x-radiation (2,000 rads, 150 kV) in *Drosophila* oocytes are characterized by a random intercellular distribution. Thus, the ionizations produced by x-radiation represent a good example of randomly distributed mutagenic events. (13 refs)

- 79-6366 Absence of Ecotropic or Recombinant Murine Leukaemia Virus in Preleukaemic and Leukaemic X-Irradiated NZB Mice. (Eng) Harvey, J. J. (MRC Clinical Res. Centre, Harrow, Middlesex, England); Tuffrey, M.; Holmes, H. C.; East, J. *Int J Cancer* 24(3): 373-376; 1979.

NZB mice, which do not normally harbor any detectable ecotropic murine leukemia virus (MuLV) and rarely develop lymphocytic leukemia and/or thymic lymphomas spontaneously, were x-irradiated with a single dose of 630 rads when they were 1 mo old. Eight sick leukemic mice were killed 12-29 wk after irradiation, and eight apparently healthy preleukemic mice were killed 1 mo after irradiation. Bone marrow, spleen, and thymus from these animals were co-cultivated with selectively permissive cell lines, followed by the immunofluorescence test for MuLV-group-specific (MuLVgs) antigen, and the XC test. Xenotropic MuLV, but no ecotropic MuLV, was detected in tissues of both irradiated and control mice. The bone marrow consistently produced most xenotropic MuLV, and the thymus least, regardless of the status of the mice examined. These results do not support the theory that x-irradiation-induced lymphocytic leukemia in NZB mice is caused by the activation of ecotropic or recombinant MuLV. (21 refs)

- 79-6367 Partial Deletion of Chromosome #2 in Myelocytic Leukemias of Irradiated C3H/He and RFM Mice. (Eng) Hayata, I. (Natl. Inst. Radiological Sciences, 4-9-1 Anagawa, Chiba 260, Japan); Ishihara, T.; Hirashima, K.; Sado, T.; Yamagiwa, J. *J Natl Cancer Inst* 63(3): 843-848; 1979.

The chromosomes of seven mice (3 C3H/He males, 1 RFM female, and 3 RFM males) that developed myelocytic leukemias after whole-body irradiation were analyzed using chromosome-banding techniques. Chromosomes number 2 were partially deleted in six mice. Although the deleted number 2 chromosomes varied in size in these mice, one common characteristic was noted in all these deletions: a segment lying between a certain band in the region 2C and a band in the region 2E, including the whole region 2D, was missing. Another consistent abnormality was an addition or a loss of the Y-chromosomes in the fraction of cells in all six males. The RFM female, which had the normal 2 chromosome, had structural abnormalities in chromosomes number 3, 4, 10, 11, 12, and 15 and in the X-chromosome. Of the 20 chromosome pairs, only such chromosomes as 1, 5, 8, 14, 17, and 19 and the Y-chromosome did not have structural abnormalities. The possible role of the partial deletion of the number 2 chromosome was considered in relation to the development of mouse myeloid leukemias. (13 refs)

- 79-6368 Thyroid Neoplasia Following Irradiation for Medulloblastoma: Report of Two Cases. (Eng) Roggli, V. L. (Dept. Pathology, Baylor Coll. Medicine, 1200 Moursund, Houston, TX 77030); Estrada, R.; Fechner, R. E. *Cancer* 43(6): 2232-2238; 1979.

The case reports of two patients (women aged 42 and 22 yr) who developed thyroid neoplasms 14 and 18 yr after treatment with radiation for medulloblastoma are given. One patient had a papillary cancer and the other (the 22-yr-old woman) had multiple adenomas and a Hurthle cell adenoma. In addition, the latter patient had foci of hyperplasia plus a microfollicular transformation that has not been described in association with prior thyroid irradiation. The radiation doses delivered to the thyroid through posterior cervical spinal ports (2,000-3,000 R) fall within the upper range of radiation dosage associated with induction of neoplastic changes within the thyroid. (19 refs)

- 79-6369 Anaplastic Carcinoma of the Thyroid Following External Irradiation. (Eng) Getaz, E. P. (Southeastern Massachusetts Medical Associates, 322 E. Center St., W. Bridgewater, MA 02379); Shimaoka, K.; Rao, U. *Cancer* 43(6): 2248-2253; 1979.

Two cases of anaplastic carcinoma following irradiation of Hodgkin's disease (HD) are reported. A 49-yr-old man was treated at age 5 with 290 rads to the neck for a swelling of 2 yr duration that had been diagnosed as HD. He had also received 12 x-ray treatments from his physician (dosimetry unknown). The patient had smoked heavily for many years prior to the diagnosis and removal of a highly anaplastic thyroid tumor 44 yr later. A 54-yr-old man with severe Coombs-positive hemolytic anemia had been irradiated several times over the previous 19 yr for recurrent lymphadenopathy due to HD. Twelve yr later, he presented with facial and neck pain, dysphagia, and a choking sensation. He was found to have a highly undifferentiated thyroid carcinoma and a bloody pleural effusion secondary to pulmonary metastases. At autopsy, several tumor nodules were found in both the lungs and liver, and

the mediastinal and abdominal lymph nodes were enlarged. The liver nodules and abdominal lymph nodes showed only HD. Eleven other patients with thyroid cancer following irradiation have been reported. The mean age of these patients was 52.4 yr, and the mean latent period was 27.38 yr. Patients with early HD who have undergone irradiation, especially of the neck and mediastinum, must be considered at risk for the development of thyroid malignancy for the rest of their lives. (44 refs)

- 79-6370 Lymphangiosarcoma Arising From Lymphangioma Circumscriptum. (Eng) King, D. T. (Dept. Pathology, Los Angeles County Harbor-UCLA Medical Center, Torrance, CA); Duffy, D. M.; Hirose, F. M.; Gurevitch, A. W. *Arch Dermatol* 115(8): 969-972; 1979.

The development of a lymphangiosarcoma at the site of a preexisting lymphangioma circumscriptum on the lower part of the abdominal wall in a 43-yr-old woman is reported. Approx 15 yr prior to the development of the malignant tumor, this area had received extensive x-irradiation (2,400 rad) during a course of radiotherapy for squamous cell carcinoma of the uterine cervix. The malignant vascular neoplasm found in the abdominal wall was classified as a lymphangiosarcoma because of the presence of lymphatic-type channels and absence of blood cells within the lumina. This is only the second such case to be reported, the first patient also having been exposed to substantial x-ray therapy prior to the development of lymphangiosarcoma. X-irradiation may play a role in the development of this unusual malignant neoplasm, and it seems advisable to avoid exposure of lymphangioma circumscriptum to substantial amounts of radiation. (17 refs)

- 79-6371 Dose Conversion Factors for Radon Daughters. (Eng) Walsh, P. J. (Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). *Health Phys* 36(5): 601-609; 1979.

Dose-conversion factors consistent with present epidemiological, toxicological, and theoretical evidence about radiogenic lung cancer are suggested for short-lived radon daughters. These dose-conversion factors are based upon risk estimates derived from epidemiological studies that have demonstrated an association between exposure of the lung to ionizing radiation and lung cancer. Various risk estimators, including absolute risk, relative risk, percent increase in excess cases, and excess cases as a fraction of observed cases, are compared. The nature of risk per unit exposure as a function of exposure is shown to be dependent on the risk estimator used. The hypothesis that the excess of observed cases over expected cases is directly proportional to exposure is supported in the range of available data. The nature of exposure response relationships at low exposures is uncertain because of uncertainties in individual exposure estimates. Risks could be overestimated or underestimated depending on the risk estimator used when exposures approach background exposures, especially if background exposures are not included in exposure estimates. (24 refs)

- 79-6372 Collagen Localization in Lung Parenchyma Irradiated by Inhaled $^{239}\text{PuO}_2$ Particles. (Eng) Diel, J. H. (Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM 87115); Short, R. K. *Radiat Res* 79(2): 417-423; 1979.

The location of the increased lung collagen which has been shown to result from radiation injury to the lung relative to the radiation source was studied. Seven-wk-old Syrian hamsters were exposed by inhalation to a monodisperse aerosol of $^{239}\text{PuO}_2$ particles and sacrificed 136 days later. Excess collagen was found around 6/7 isolated plutonium particles of a single lung. The excess collagen extended to distances of 100-400 μm , averaging $1.6 \pm 0.5 \times$ the background collagen level over a region within 300 μm of the particle. The collagen accumulation within an area containing numerous plutonium particles showed a general increase corresponding to $2.6 \times$ the background level. These regions with numerous particles were invariably associated with foci of obvious structural damage and accumulations of macrophages and other cells and cellular debris. About 30% of the $^{239}\text{PuO}_2$ particles were associated with these foci. The total amount of collagen in the lung as a fraction of the total collagen in a normal lung was estimated to be 1.23. For a given amount of α -emitting material, the effect on lung function due to increased compliance and decreased gas transfer should be less for material contained in a few large particles than for material uniformly distributed throughout the lung. (9 refs)

- 79-6373 Kinetics of Plutonium-239 Metabolism and Absorbed Doses in Dogs after Inhalation Exposure. (Rus) Buldakov, L. A. (No affiliation given); Kalmykova, Z. I. *Radiobiologiya* 19(3): 408-412; 1979.

This study was designed to evaluate the kinetics of plutonium-239 metabolism in dogs after a single inhalation exposure. Polymeric ^{239}Pu was given intratracheally to mongrel dogs at doses of 0.1-10 $\mu\text{Ci}/\text{mg}$. It was found that 11% of the radioactivity was eliminated from the lungs within 1 day of exposure, 22.2% within 103 days, and 94.8% within 2,100 days (the half-life was 555 days). The radionuclide was retained in most of the internal organs for 300-800 days, whereas retention in the skeleton, liver, kidneys, and heart lasted up to 2,100 days. By day 2,100 after exposure, the level of radionuclide in the skeleton and liver was 2.5 and 3 times greater than that in the lungs. Daily excretion of ^{239}Pu in the feces and urine constituted 0.035%-0.15% and 0.021%-0.25% of the overall amount of the radionuclide in the lungs, respectively. There was no correlation between ^{239}Pu levels in the lungs or liver and the amount excreted. (7 refs)

- 79-6374 Isolation and Characterization of Individual Plutonium-bearing Particles in Atmospheric Effluents from a Nuclear Processing Plant. (Eng) Sanders, S. M. (Savannah River Lab., E. I. du Pont de Nemours and Co., Aiken, SC 29801). *Health Phys* 36(3): 371-385; 1979.

A method for isolating and characterizing individual particles containing fissionable materials is described. Membrane filters, used to collect the particles from atmospheric effluents from a nuclear processing plant, are cast into films composed of a polycarbonate matrix containing the particles. Collected particles containing plutonium or other fissionable materials are identified by fission fragment tracks produced by irradiating the film with thermal neutrons. The nature of the fissionable material is identified by coating the film with nuclear track emulsion and measuring the ratio of alpha particle tracks in the emulsion to the fission fragment tracks in the polycarbonate film. Single particles are isolated by excising small squares from the film and are prepared for sizing and electron microbeam analysis by peeling the emulsion off the film square, placing the square on a beryllium sample-mounting

block, and washing the polycarbonate away from the particle. (15 refs)

- 79-6375 Kinetics of Americium-241 Metabolism and Absorbed Doses in Dogs after Inhalation Exposure. (Rus) Buldakov, L. A. (No affiliation given); Kalmykova, Z. I. *Radiobiologiya* 19(3): 462-467; 1979.

The long-term effects of exposure to americium-241 were studied in mongrel dogs. The radionuclide was given intratracheally at doses of 1-100 μCi ; the metabolism of ^{241}Am was monitored for 6.5 yr after a single exposure. Most (54.5%) of the inhaled dose was deposited in the bones. Elimination of the radionuclide from the lung tissue could be described by a three-exponent equation: 54% of the administered radioactivity was eliminated at a constant rate of 0.956 days^{-1} , 17.5% at a rate of 0.0352 days^{-1} , and 5.2% at a rate of $0.00067 \text{ days}^{-1}$ (the half-lives were 0.752, 19.7, and 1,035 days, respectively). The half-life of the radionuclide in the feces and urine was 795 and 950 days, respectively (25.3% and 26.5% of the radioactivity was eliminated in the feces and urine over a period of 2,443 days). The absorbed doses were max in the lungs, lymph nodes, liver, and bones. (7 refs)

- 79-6376 Anaplastic Astrocytoma Following Radiation for a Glomus Jugulare Tumor. (Eng) Preissig, S. H. (Dept. Pathology, Duke Medical Center, Durham, NC 27710); Bohmfalk, G. L.; Reichel, G. W.; Smith, M. T. *Cancer* 43(6): 2243-2247; 1979.

A 43-yr-old man was given 4,480 rads to the right middle and inner ear and temporal bone for a glomus jugulare tumor of the right middle ear. Eight yr later, he developed an anaplastic astrocytoma of the right cerebellar hemisphere. At this time, a third neoplasm, a left carotid body tumor, was demonstrated angiographically. Although radiation can be implicated in the genesis of the glial neoplasm, the presence of two neural crest-derived tumors suggests that a lowered threshold for neoplastic transformation in neuroectodermal cells may have been an additional factor. Long-term follow-up of large numbers of patients with glomus jugulare tumors will be necessary to determine if multiple paragangliomas predispose to radiation-associated gliomas. (37 refs)

- 79-6377 Defective Reactivation of Ultraviolet Light-irradiated Herpesvirus by a Bloom's Syndrome Fibroblast Strain. (Eng) Selsky, C. A. (Dept. Biological Sciences, Stanford Univ., Stanford, CA 94305); Henson, P.; Weichselbaum, R. R.; Little, J. B. *Cancer Res* 39(9): 3392-3396; 1979.

The technique of host cell reactivation of UV-irradiated herpes simplex virus type 1 was used as a measure of the repair capacity of three Bloom's syndrome skin fibroblast strains. At a low multiplicity of infection ($<6 \times 10^{-4}$ plaque-forming unit/cell), reactivation of the virus by the Bloom's syndrome strains was indistinguishable from that by normal strains. Reactivation at higher multiplicities was measured using an infectious centers assay. At 3 plaque-forming units/cell, survival of UV-irradiated herpes simplex virus was higher in all cell strains as a result of the multiplicity reactivation effect. This effect was, however, much smaller in one Bloom's syndrome strain, GM1492, than in either the normal strains or the other Bloom's syndrome fibroblasts. The defect in GM1492 was manifest only at relatively high

multiplicities of infection. Thus, at 0.01 plaque-forming unit/cell, the GM1492 strain appeared normal, using the infectious centers assay. Clonal survival of the UV-irradiated GM1492 fibroblasts was also normal. Caffeine (4 millimolar) had little effect on either virus or cell survival following UV irradiation. The results indicate that Bloom's syndrome strain GM1492 may be deficient in one of the cellular functions responsible for the multiplicity reactivation effect. These effects include complementation and recombinational events. Alternatively, the GM1492 strain may have a defective UV repair system that becomes saturated at high levels of damage. (22 refs)

- 79-6378 **Hyperplasia and Neoplasia of the Intestinal Tract.**
(Eng) Williamson, R. C. (Dept. Surgery, Univ. Bristol, Bristol, England). *Ann R Coll Surg Engl* 61(5): 341-348; 1979.

Mucosal hyperplasia in the remaining gut within 48 hr of partial intestinal loss was investigated using male Sprague-Dawley and Fischer rats. Jejunal transection caused a transient burst of hyperplasia, whereas jejunal resection resulted in an intense and prolonged cell proliferation. Both transection and resection resulted in increased RNA, DNA, and DNA specific activity in the mid-bowel mucosa of parabionts who had undergone abdominal operations, whereas only DNA specific activity was markedly increased in intact parabionts. Elevations in ileal RNA and DNA shortly after jejunal resection exceeded those seen shortly after jejunal bypass, but the responses 1 mo after either procedure were

indistinguishable. Colonic RNA and DNA increased moderately after resection but remained unchanged or even decreased after bypass. Bypass produced prompt and progressive hypoplasia in the mucosa of the excluded jejunal segment. Ileal mucosal DNA and RNA were elevated 48 hr and 1 wk after distal diversion of bile and, to a greater extent, after pancreatobiliary diversion. Values returned to normal thereafter in rats with bile diversion alone but rose progressively after diversion of both secretions. Diversion caused limited increases in colonic nucleic acids and no lasting changes in jejunal values. Azoxymethane (AOM, 10 mg/kg/wk, sc, for 16 wk) caused jejunal hyperplasia followed by the appearance of macroscopic intestinal tumors, and proximal enterectomy alone resulted in ileal hyperplasia which persisted for 3 mo. The number of AOM-induced small bowel tumors per rat was not affected by surgery, but proximal small-bowel resection significantly increased the number of colonic tumors per rat ($p < 0.02$). (21 refs)

See also:

- *(Rev.): 79-6035, 79-6067, 79-6068, 79-6069, 79-6070, 79-6071, 79-6111, 79-6113.
- *(Chem.): 79-6139, 79-6191, 79-6231, 79-6287.
- *(Viral): 79-6392, 79-6408, 79-6458.
- *(Immun.): 79-6494, 79-6497, 79-6515, 79-6517, 79-6518.
- *(Path.): 79-6529.
- *(Epid.-Biom.): 79-6569, 79-6570, 79-6576.

VIRAL CARCINOGENESIS

- 79-6379 Effect of Viral RNase H on the Avian Sarcoma Viral Genome During Early Transcription In Vitro. (Eng) Friedrich, R. (Inst. Tumormmunology, Univ. Freiburg, D-7800 Freiburg, W. Germany); Moelling, K. *J Virol* 31(3): 630-638; 1979.

The influence of viral RNase H on the transcription of the avian sarcoma virus RNA in a virion-associated reaction was investigated. The ability of RNase H to degrade the RNA moiety of the initially formed RNA-DNA hybrid at the 5' end of the viral genome was greatly dependent on the exact concentration of non-ionic detergent used to activate the reaction. At a detergent concentration optimal for extensive and faithful in vitro transcription of avian sarcoma virus RNA by the virion-associated RNA-dependent DNA polymerase, most of the 5' terminus of the RNA was digested in 30 min at 41 C. At higher than optimal detergent concentrations, however, little of that RNA was digested. It was concluded that removal of the 5'-terminal redundancy in the RNA after its transcription into DNA is a prerequisite for base pairing of the DNA to the 3'-terminal redundant sequence; lack of removal of this sequence leads to incorrect elongation and substantial reduction of DNA synthesis. When tested with a synthetic RNA-DNA hybrid, virion-associated RNase H did not reveal a detergent dependence. (51 refs)

- 79-6380 Virus-specific Messenger RNAs in Permissive Cells Infected by Avian Sarcoma Virus. (Eng) Lee, J. S. (Dept. Microbiology and Immunology, Univ. California, San Francisco, CA 94143); Varmus, H. E.; Bishop, J. M. *J Biol Chem* 254(16): 8015-8022; 1979.

The viral RNA contained in total, membrane-bound, and free polyribosomes isolated from chicken cells infected with wild type avian sarcoma virus (ASV) or deletion mutants of ASV was characterized. The 38S and 21S RNAs, which are presumed to be the messengers for the viral genes *gag/pol* and *src*, respectively, were found largely or entirely in the free polyribosomes. The 28S RNA was contained predominantly in membrane-bound polyribosomes, where it apparently serves as messenger for the viral gene *env*. No additional virus-specific RNAs were identified in either polyribosomes or cytoplasmic extracts. In particular, previous reports of a viral RNA smaller than the 21S species were not confirmed, and no viral RNA that might contain the gene *pol* at its 5' terminus was found. It is concluded that permissive cells infected with ASV contain three major classes of viral mRNA. The glycoprotein product of *env* is synthesized on membrane-bound polyribosomes and is presumably the only integral membrane protein. The products of the other viral genes are synthesized on free polyribosomes and are neither integral membrane proteins nor secretory proteins. (45 refs)

- 79-6381 Cells Transformed by Temperature-Sensitive Mutants of Avian Sarcoma Virus Cause Tumors in Vivo at Permissive and Nonpermissive Temperatures. (Eng) Poste, G. (Dept.

Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263); Flood, M. K. *Cell* 17(4): 789-800; 1979.

The tumorigenicity of chick embryo (CE) fibroblasts and normal rat kidney (NRK) cells transformed by temperature-sensitive (*ts*) mutants of avian sarcoma virus (ASV) was tested in the chorioallantoic membrane (CAM) of chick eggs, and the resulting tumors were characterized. CE and NRK cells transformed by *ts* mutants of ASV (NY68, LA23, LA24, LA25, LA31, G1201, G1202, G1251, G1253) induced tumors on the CAM at temperatures corresponding to the permissive (35 C) and nonpermissive (41 C) conditions used to induce conditional expression of "transformed" properties in these cells when cultured in vitro. Chick embryo cells infected with transformation-defective mutants of ASV (td101, td108) or RAV-50 were nontumorigenic under the same conditions, as were nontransformed CE and NRK cells. This indicates that the CAM is not an unusually susceptible substrate for cell growth and that the ability of *ts*ASV-transformed cells to form tumors at nonpermissive temperatures reflects their true tumorigenicity. In contrast, a *ts* mutant chemically transformed rat liver cell line, ts-223, only formed tumors on the CAM under permissive conditions. The wild-type parent cells (W-8) of this mutant produced tumors at both permissive and nonpermissive temperatures. Direct implantation of microprobe thermometers into tumors caused by *ts*ASV-transformed cells at nonpermissive temperatures confirmed that tumor formation occurred in a stable temperature environment and was not due to temperature fluctuations, which might have created semi-permissive or permissive conditions for tumor growth. Cells isolated from tumors formed at nonpermissive temperatures and recultured in vitro displayed temperature-dependent hexose transport and colony formation in agar similar to the original parent cell inoculum. Similarly, virus recovered from tumors at nonpermissive temperatures retained the *ts* mutation. (52 refs)

- 79-6382 A Normal Cell Protein Similar in Structure and Function to the Avian Sarcoma Virus Transforming Gene Product. (Eng) Collett, M. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO 80262); Erikson, E.; Purchio, A. F.; Brugge, J. S.; Erikson, R. L. *Proc Natl Acad Sci USA* 76(7): 3159-3163; 1979.

A protein from normal cells that is closely related to the avian sarcoma virus (ASV) transforming gene product pp60^{src} was further characterized. This normal cellular protein, which was found in both avian and mammalian cells and was tentatively designated pp60^{src}, was detected by immunoprecipitation of radiolabeled cell extracts with serum derived from both mice and rabbits bearing ASV-induced tumors. The normal cell pp60^{src} is a 60,000-dalton phosphoprotein that is structurally similar, but not identical, to viral pp60^{src}. The phosphorylation patterns of the normal cell and viral proteins are also similar: both contain two major phosphorylated residues, a phosphoserine located on the NH₂-terminal 60% of the polypeptide and a phosphothreonine present on the COOH-terminal 40% of the molecule. In addition, the normal cell pp60^{src} from both chicken and mammalian cells

appears to have an associated protein kinase activity analogous to that previously described for the viral pp60^{src}. The normal cell protein pp60^{src} and the ASV transforming protein pp60^{src} may be involved in normal cellular growth and neoplastic disease, respectively. (28 refs)

- 79-6383 Characterization of an Immune Complex Kinase in Immunoprecipitates of Avian Sarcoma Virus-transformed Fibroblasts. (Eng) Richert, N. D. (Div. Cancer Biology and Diagnosis, Lab. Molecular Biology, NCI, Bethesda, MD 20205); Davies, P. J.; Jay, G.; Pastan, I. H. *J Virol* 31(3): 695-706; 1979.

Kinase activity detected in immune complexes containing the *src* gene product of the avian sarcoma virus (ASV) was characterized using trichloroacetic acid precipitation on filters. The enzyme reaction required either Mg²⁺ or Mn²⁺, but was inactive with Ca²⁺. The kinetics of the phosphorylation reaction indicated a transient enzyme activity limited by rapid substrate-dependent inactivation of the enzyme. A variety of nucleoside and deoxyribonucleoside triphosphates (dATP, ATP, GTP, dGTP, TTP, dCTP) served as phosphoryl donors. The phosphorylation of IgG was inhibited by the presence of nucleoside diphosphate, and deoxyribonucleoside diphosphates could either stimulate or inhibit the kinase reaction depending on the concentration used. The unusual enzymatic properties of the immune complex kinase raise the possibility that the enzyme does not function as a protein kinase in vivo, but rather may belong to a different class of kinases (nucleotide kinases) which phosphorylate IgG when immunoprecipitated with immune serum. (37 refs)

- 79-6384 Avian Erythroblastosis Virus: Transformation-specific Sequences from a Contiguous Segment of 3.25 kb Located in the Middle of the 6-kb Genome. (Eng) Lai, M. M. (Dept. Microbiology, Univ. Southern California, Sch. Medicine, 2011 Zonal Ave., Los Angeles, CA 90033); Hu, S. S.; Vogt, P. K. *Virology* 97(2): 366-377; 1979.

Several foci of chicken embryo fibroblasts transformed by avian erythroblastosis virus (AEV) strain ES-4 produced virus progeny containing the RNA of the replication-defective AEV in excess of the helper virus RNA. The size of AEV RNA was determined by methylmercury-agarose gel electrophoresis and electron microscopy to be 28S or 6 kilobases (kb). About 40% to 45% of this RNA was homologous by RNA-DNA hybridization to the RNA of other chicken leukosis and sarcoma viruses; the rest of the genome was AEV specific. These AEV specific sequences, which presumably contain the genetic information responsible for transformation, formed a contiguous stretch of 3.25 kb, located by heteroduplex mapping in the center of the 6 kb genome; on either side were the two segments (1.06 kb at the 3' end and 1.64 kb at the 5' end) which were homologous to the genome of avian sarcoma virus. From the length of the region showing homology between AEV and avian sarcoma virus at the 5' end of the genome and from the known sequence composition of the AEV-specific 75K protein, it can be deduced that the initiation point for the N terminus of the *gag* protein p19 is located about 1.0 kb from the 5' end of the genome in avian oncoviruses. Nonproducing AEV-transformed chicken embryo fibroblasts were also isolated. Infectious AEV could be rescued from these cells only with chicken leukosis viruses; unrelated avian retroviruses were ineffective, probably because AEV requires complementation in the *gag* and *pol* genes, in addition to *env*. (43 refs)

- 79-6385 Proliferation of Rous Sarcoma Virus-infected, But Not of Normal, Chicken Fibroblasts in a Medium of Reduced Calcium and Magnesium Concentration. (Eng) Balk, S. D. (Dept. Pathology, Faculty Medicine, Univ. Manitoba, Winnipeg, Manitoba, Canada R3E 0W3); Polimeni, P. I.; Hoon, B. S.; LeSturgeon, D. N.; Mitchell, R. S. *Proc Natl Acad Sci USA* 76(8): 3913-3916; 1979.

The roles of calcium and magnesium in the initiation of cell replication were studied. In the presence of a physiological concentration of magnesium, reduction of the calcium concentration from a physiological level (1.2 mM) to 0.125 mM resulted in a significant decrease in the proliferation of normal chicken embryo fibroblasts, but not of neoplastic, Rous sarcoma virus-infected fibroblasts. Reduction of the magnesium concentration to 0.05 mM in the presence of a physiological concentration of calcium had a similar effect. In a culture medium containing reduced concentrations of both calcium (0.20 mM) and magnesium (0.05 mM), normal fibroblasts were maintained without proliferation, whereas Rous sarcoma virus-infected fibroblasts continued to proliferate actively. The cytosol concentrations of ionized calcium and magnesium are known to be regulated by a balance between net passive influx and active extrusion and sequestration. On the basis of this consideration and the present findings, it is hypothesized that: (1) fibroblast replication is initiated when cytosolic concentrations of calcium, magnesium, or both rise above a critical level. (2) Autonomous initiation of replication of neoplastic fibroblasts is a result of failure of cytoplasmic divalent cation homeostasis; alternatively, sarcoma virus infection may endow cells with a divalent cation-independent mechanism that bypasses an initiation mechanism that is, normally, divalent cation-dependent. (3) Proliferation of normal fibroblasts is controlled by extracellular matrix components that interact with cell surfaces in a manner that limits the permeability of plasma membranes to divalent cations or otherwise functions to lower cytosol divalent cation concentrations. (28 refs)

- 79-6386 Morphological Revertants of an Avian Sarcoma Virus-transformed Mammalian Cell Line Exhibit Tumorigenicity and Contain pp60^{src}. (Eng) Lau, A. F. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Krzyzek, R. A.; Brugge, J. S.; Erikson, R. L.; Schollmeyer, J.; Faras, A. J. *Proc Natl Acad Sci USA* 76(8): 3904-3908; 1979.

The biological and biochemical properties of Rous sarcoma virus-transformed and revertant field vole cells were investigated. Revertant vole cells appear morphologically similar to normal, uninfected cells, yet, like transformed vole cells, they are fully capable of growing in agar suspension and producing tumors in athymic nude mice. These highly tumorigenic, yet morphologically normal appearing, vole cells express viral-specific antigens such as the *gag* gene product (Pr76) but lack the *env* gene protein (gp85). Moreover, they contain the *src* gene protein, pp60^{src}. These results support the concept of the pleiotropic nature of the *src* gene product and in addition suggest that pp60^{src} may have multiple mechanisms of action. With this revertant cell system it may be feasible to distinguish between those biochemical functions of the *src* gene product that are important for tumorigenicity in vivo and those that are related to in vitro morphological transformation. (26 refs)

- 79-6387 Regulation of the Proliferative Response in Rous Sarcoma Virus Transformed Chicken Embryo

Fibroblasts by Serum and Multiplication-stimulating Activity (MSA). (Eng) Knauer, D. J. (Sch. Life Sciences, Univ. Nebraska, Lincoln, NE 68588); Smith, G. L. *J Cell Physiol* 100(2): 311-322; 1979.

The growth stimulatory response of transformed chicken embryo fibroblasts to serum and purified multiplication-stimulating activity (MSA), a polypeptide growth factor, was investigated. A temperature sensitive mutant of Rous sarcoma virus (tsNY68) was used to obtain cultures of quiescent virus-infected chicken embryo fibroblasts arrested by serum starvation at the nonpermissive temperature. Upon shift to the permissive temperature, these cells enter the replicative cell cycle. These changes occur in the absence of serum, and the cells become morphologically transformed within 8-10 hr after the temperature shift. Entry into the S phase temporally resembles that of normal quiescent fibroblasts stimulated with serum. The presence of serum in the medium enhanced the proliferative response of quiescent infected cells shifted to the permissive temperature over those shifted in the absence of serum. In contrast, infected cultures shifted in the presence of MSA showed no significant increase in cell number above that of cultures shifted in serum-free medium. Labeled MSA binding experiments showed that this lack of response was not due to a loss of MSA receptors on the cell surface, since transformed cells were still capable of binding MSA at the same level as normal cells. The results are consistent with the hypothesis that the set of biochemical events initiated by MSA in normal cells are turned on in infected cells shifted to the permissive temperature by the activation of the src gene product. (33 refs)

79-6388 Embryonal and Tumor-specific Plasma Membrane Antigens of Rous Sarcoma Virus Transformed Fibroblasts. (Eng) Prat, M. (Cattedra di Istologia e Embriologia, Università di Trieste, Trieste, Italy); Tarone, G.; Comoglio, P. M. *Ital J Biochem* 28(2): 124-127; 1979.

The antigenic composition of baby hamster kidney (BHK)-C13/21 fibroblasts transformed by Rous sarcoma virus (RSV; B46 cells) was investigated using antisera raised in rabbits immunized with B46 cells. When the serum was adsorbed with normal hamster cells (C13 cells), it had no cytotoxic activity against them but killed hamster cells transformed by murine sarcoma virus (MuSV), simian virus 40, polyoma virus, and RSV; a common tumor-associated antigen thus appears to be expressed on all the transformed hamster cells. Ten-day-old hamster embryo cells were perfectly lysed by the anti-B46/C13 adsorbed serum. This indicates that, following viral transformation, a cellular gene silent in normal cells is derepressed. Anti-B46/C13 adsorbed sera which were further adsorbed with polyoma virus-transformed cells had no cytotoxic activity to MuSV- or polyoma virus-transformed cells but still reacted with B46 cells. Thus B46 cells express a second tumor antigen, VCSA (virus cell surface antigen), which is specifically induced by the transforming virus. RSV-transformed quail and chicken cells were also lysed by the anti-VCSA sera, while uninfected chick embryo fibroblasts and chick embryo fibroblasts infected by a transformation-defective mutant of RSV were not lysed. Thus VCSA expression is under the control of the RSV genome and is not a virion structural protein. (6 refs)

79-6389 Shedding of Hyaluronate from the Cell Surface of Rous Sarcoma Virus-transformed Chondrocytes. (Eng) Mikuni-Takagaki, Y. (Developmental Biology Lab., Massachusetts General Hosp., Boston, MA 02114); Toole, B. P. *J Biol Chem* 254(17): 8409-8415; 1979.

Transformation of cultured chick embryo chondrocytes with Rous sarcoma virus increased incorporation of isotopic precursors into hyaluronate and decreased incorporation into chondroitin 6-sulfate. Chemical measurements of these glycosaminoglycans showed corresponding changes. Comparison of the kinetics of glycosaminoglycan production by normal and Rous sarcoma virus-transformed chondrocytes demonstrated that the rate of accumulation in the medium was similar in both cultures and that approx 50% of total glycosaminoglycan produced by the normal chondrocytes, but only 10% of that from the transformed cells, accumulated in the cell layer. Prelabel-chase experiments indicated that cell surface-associated hyaluronate, as measured by release from the cell layer by trypsin treatment, was shed rapidly into the medium and accounted for all of the hyaluronate which accumulated there. It was concluded that accumulation of cell surface-associated glycosaminoglycan is dramatically reduced in Rous sarcoma virus-transformed chondrocytes and that hyaluronate produced by the transformed chondrocytes is first deposited in the cell-associated extracellular compartment and then rapidly shed into the medium, rather than being secreted directly into the medium. (67 refs)

79-6390 Avian Sarcoma Virus Envelope Glycoprotein (gp85) Specifically Binds Chick Embryo Fibroblasts. (Eng) Moldow, C. F. (Dept. Medicine, Univ. Minnesota Sch. Medicine, Minneapolis, MN 55455); Reynolds, F. H.; Lake, J.; Lundberg, K.; Stephenson, J. R. *Virology* 97(2): 448-453; 1979.

The binding of ¹²⁵I-labeled highly purified Prague (Pr) strain Rous sarcoma virus (RSV) subgroup C envelope glycoprotein (gp85) to C/E chicken embryo fibroblasts (CEF) was linear with respect to gp85 concentration and relatively independent of temperature between 4 C and 37 C. At saturation 1 x 10⁵ to 2 x 10⁵ molecules of gp85 were bound per cell. Genetically resistant C/C CEF bound considerably less glycoprotein. The specificity of the binding activity was indicated by the fact that neither C/E nor C/C CEF exhibited detectable binding of Rauscher murine leukemia virus envelope glycoprotein (gp70). Of the avian viruses tested, only those with subgroup C host range inhibited binding of ¹²⁵I-labeled Pr-RSV-C gp85 by C/E CEF. These findings indicate that Pr-RSV-C gp85 can be purified with retention of biological binding activity and may be a useful reagent for further analysis of the early events of avian RNA tumor virus infection. The use of this reagent should make possible the purification and analysis of cellular receptor sites for avian type C viral envelope glycoproteins. (13 refs)

79-6391 Alignment of the Restriction Map of Mouse Adenovirus FL with that of Human Adenovirus 2. (Eng) Larsen, S. H. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205); Margolske, R. F.; Nathans, D. *Virology* 97(2): 406-414; 1979.

A restriction map of mouse adenovirus strain FL (AdFL) was constructed based on sites of cleavage of AdFL DNA by 19 restriction endonucleases. The AdFL map was oriented with respect to that of human adenovirus type 2 (Ad2) by identifying which end of AdFL DNA is retained in virions with incomplete genomes compared with the end retained by Ad2 defective particles as previously determined. The AdFL map was also oriented to that of Ad2 by locating small regions of DNA homology in the AdFL and Ad2 cleavage maps. Cross-hybridization tests with a series of restriction fragments of each viral DNA revealed two regions of homology between Ad2 and AdFL DNA, which corresponded to the posi-

tions of the Ad2 hexon gene and an Ad2 hexon-associated protein gene. The regions of homology between the hexon genes of AdFL and Ad2 are more extensive than between the genes for hexon-associated protein. (12 refs)

- 79-6392 Ultraviolet Radiation Induction of Endogenous Murine Type C Virus. (Eng) Hellman, K. B. (Bureau Radiological Health, FDA, Rockville, MD 20857); Brewer, P. P. *Mutat Res* 62(2): 205-212; 1979.

The dose-response relationship for UV induction of mammalian type C virus was studied using the A1-2 cell line, a clonal sarcoma-positive, helper-negative derivative of adult BALB/c mouse peritoneal cells transformed by Gazdar murine sarcoma virus. Irradiation of log-phase A1-2 cells induced endogenous xenotropic type C virus, as determined by MSV focus assay on NRK cells. Induction was observed from 24 to 72 hr, with optimal induction occurring at 48 hr. The number of virus-induced cells increased with radiation exposure, reaching an optimal fourfold increase at 2 J/m² and decreasing with higher radiation doses. Although the fraction of A1-2 cells induced to release virus by UV radiation (0.17%) was less than that observed after treatment with 5-iodo-2-deoxyuridine (3.0%) or 5-bromo-2-deoxyuridine (0.46%), the use of the sensitive infectious center assay demonstrated reproducible UV induction. Examination of A1-2 cell survival following irradiation showed that optimum viral induction occurred at a UV exposure corresponding to the edge of the shoulder of the survival curve, suggesting that UV sensitivity of the host cell may be a factor limiting the level of induction. Since less radiation was required for viral induction than for inactivation of colony-forming ability, viral induction may be a more sensitive dosimeter of in vitro UV bioeffects than cell survival for this system. (26 refs)

- 79-6393 Generation of a Mouse Mammary Tumor Virus (MMTV) Pseudotype of Kirsten Sarcoma Virus and Restriction of MMTV *gag* Expression in Heterologous Infected Cells. (Eng) Schochetman, G. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Long, C.; Massey, R. *Virology* 97(2): 342-353; 1979.

C3H mouse mammary tumor cells producing mouse mammary tumor virus (MMTV) were cocultivated with nonproducer mouse cells (KNIH) transformed by Kirsten sarcoma virus (KiSV). These cocultivated cells were then treated with mitomycin C and overlaid onto human embryonic skin and muscle cells. The virus resulting from this cocultivation could be titrated in a focus-forming assay on Fischer rat embryo (FRE) cells exhibiting one-hit kinetics. Furthermore, focus formation on FRE cells was neutralized specifically by antiserum directed against MMTV and the major MMTV external glycoprotein gp52, but not against a broadly reactive antiserum directed murine leukemia virus (MuLV) gp70 and MMTV gp36, p27, p14, and p10. These results demonstrated the generation of a KiSV(MMTV) pseudotype; in addition, gp52 was shown to be a target antigen for neutralization of MMTV. This pseudotype possessed a wide host range, transforming cells of human, rat, mouse, mink, and rabbit origin. MMTV but not MuLV antigen expression was demonstrated in the KiSV(MMTV) pseudotype-infected cells. Analysis of intracellular MMTV protein synthesis in these in vitro-infected cells indicated that the low yield of extracellular MMTV produced by the transformed cells may be the result of poor expression of the MMTV *gag* precursor polyprotein relative to the expression of the *env* gene polyprotein. These studies provide the basis for an in vitro infectivity assay for neutralization and host range studies of MMTV. (23 refs)

- 79-6394 Intracisternal A Particle-specific DNA Sequences in Mammary Tumor Cells, Hybrids, and Cybrids Derived from Laboratory Mice and from Feral Mice of *Mus musculus* and *Mus cervicolor*. (Eng) Yang, S. S. (Lab. Cell Biology, NCI, Bethesda, MD 20014); Wivel, N. A. *Virology* 96(1): 166-176; 1979.

DNA sequences homologous to murine intracisternal A-particle (IAP) complementary DNA (cDNA) were examined by nucleic acid hybridization, using mammary tumor (MT) cells, hybrids, and cybrids derived from laboratory mice and from feral mice of *Mus musculus* and *Mus cervicolor*. The radioactive cDNA probe was synthesized by the endogenous reverse transcriptase reaction in purified mammary tumor IAP. Given the copy numbers of IAP-specific DNA sequences obtained in the various parent cells, hybrids, and cybrids and the thermal stability characteristics of the DNA duplexes, two distinct phenomena were observed. First, one phenotypically negative recipient cell line, 3T3-4EF, had only one to two copies of IAP-specific DNA sequences per haploid genome prior to fusion. When this line was fused to MT cytoplasts (enucleated cells) containing IAP, the resulting cybrid cells were found to have about 10 copies of IAP-specific DNA sequences, which were localized by the Hirt procedure in the detergent-insoluble fraction of the nuclear DNA. Thus, the continuous replication of IAP in the MT x 3T3-4EF cybrids was associated with an increase in the number of IAP-specific DNA sequences in the cell genome. Second, another phenotypically negative recipient cell line, 116C, had about four copies of IAP-specific DNA sequences per haploid genome prior to fusion. Following fusion with MT cytoplasts, the resulting MT x 116C cybrids did not show any increase in the number of IAP-specific DNA sequences, even after IAP replication had become overt, continuous, and nonsegregated. The distribution of DNA copies in the various *Mus musculus* and *Mus cervicolor* laboratory and feral mouse cells indicates that the IAP genome has been conserved in spite of the divergence of the two species. (32 refs)

- 79-6395 Effect of Dexamethasone on Expression of Endogenous Mouse Mammary Tumor Virus Sequences in BALB/c Tumor Cell Lines. (Eng) Dudley, J. P. (Dept. Microbiology, Univ. California Sch. Medicine, San Francisco, CA 94143); Butel, J. S. *Virology* 96(2): 453-462; 1979.

Two complementary DNA (cDNA) probes representative of either the entire mouse mammary tumor virus (MMTV) RNA genome or its poly(A)-adjacent sequences were used to monitor any changes that occur at the level of viral RNA accumulation following dexamethasone (DXS) treatment of BALB/c mammary tumor cell lines. Lines that contained only endogenous MMTV sequences responded to DXS treatment with minimal (approx 2-fold) increases in MMTV RNA. This is in marked contrast to the 10- to 20-fold increases observed with cell lines harboring exogenous MMTV variants. Comparison of hybridization results obtained with the two cDNA probes suggests that the DXS response of BALB/c lines is also qualitatively different from that of exogenous MMTV-producer cell lines. Thermal stability studies suggested a 2%-3% divergence between the RNA sequences of endogenous BALB/c and exogenous C3H viruses, with the 3' end of the viral RNA appearing to be conserved relative to the rest of the genome. (33 refs)

- 79-6396 Immunocytochemical Distribution of Mouse Mammary Tumor Virus Antigens in BALB/cC3H Mammary Epithelium. (Eng) St. George, J. A. (Dept. Anatomy, Sch.

Veterinary Medicine, Univ. California, Davis, CA 95616); Cardiff, R. D.; Young, L. J.; Faulkin, L. J. *J Natl Cancer Inst* 63(3): 813-820; 1979.

Using polyvalent anti-MuMTV serum and indirect immunoperoxidase techniques, the distribution of mouse mammary tumor virus (MuMTV) antigens was studied in normal, preneoplastic, and neoplastic mammary epithelia from female BALB/cfC3H mice. The MuMTV antigens were on the apical surface, in focal cytoplasmic aggregates, or diffused throughout the infected cells. As many as 70% of the cells in adenocarcinomas and 100% of all cells in preneoplastic hyperplastic alveolar nodules contained MuMTV antigens. Comparable percentages of cells from mammary glands of multiparous mice were MuMTV-positive. Some mammary tissues of nulliparous and primiparous mice did not contain detectable MuMTV antigen. The MuMTV antigen-containing cells in lactating mammary glands tended to be in discrete lobuloalveolar clusters surrounded by antigen-negative alveoli. The percentage of MuMTV-positive cells in a given gland was proportional to the amount of virus found in the animal's milk. (30 refs)

79-6397 In Vitro Infectivity Assay for Mouse Mammary Tumor Virus. (Eng) Vacquier, J. P. (Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616); Cardiff, R. D. *Proc Natl Acad Sci USA* 76(8): 4117-4121; 1979.

Studies of mouse mammary tumor virus (MMTV) have been impeded by the lack of an in vitro infectivity assay. A rapid, quantitative in vitro assay for MMTV infectivity based on the detection of positively staining foci by immunoperoxidase was developed. This assay and a 50% end-point titration of MMTV infectivity gave identical virus titers. Infection of a rat hepatoma cell line, a feline kidney cell line, and a normal murine mammary gland cell line by virus from the mouse mammary tumor GR3A cell line was linear with respect to virus concentration. The infectious titers obtained in both homologous and heterologous cell lines were not significantly different, demonstrating a lack of host range specificity. Virus infectivity was inactivated by heating at 55 C and by ultraviolet irradiation. Rabbit anti-MMTV serum neutralized the infectivity with a 50% neutralization end point of 1:5000. Applications of this assay to the study of the immunological, biological, and biochemical characteristics of MMTV are discussed. (25 refs)

79-6398 Levels of Mammary Tumor Virus Proteins (MTVp27 and MTVgp52) in the Milk of Low and High Mammary Cancer Mouse Strains of Japanese Origin Compared with European and American Strains. (Eng) Imai, S. (Dept. Pathology, Nara Medical Coll., 840 Shijo-cho, Kashihara-shi, Nara-Ken 634, Japan); Hilgers, J. *Int J Cancer* 24(3): 359-364; 1979.

A competition radioimmunoassay for purified murine tumor virus (MTV) proteins MTVp27_{gag} and MTVgp52_{env} was used to measure the amounts of these proteins in the milk of mice of various Japanese, European, and American strains. The SL/NiA strain was positive for MTV-p27 in the milk (10-100 nanograms(ng)/mg). Foster nursing of this Japanese strain on BALB/c mice did not lead to the disappearance of MTVp27 antigen expression, indicating that the MTV is genetically transmitted in this strain. Other high mammary cancer strains had large amounts of MTV in their milk; these included FM/JmsA [1,500-4,500 and 2,600-18,000 ng/mg milk protein of MTVp27 and MTVgp52, respectively], C57BL/6MsMtA (1,500-1,900 and

1,400-7,600 ng/ml), and DD/Tbr (470-3,300 and 670-6,700 ng/mg). These levels of MTVp27 and MTVgp52 were comparable to those of the C3H/HeA, A/BrA, and R111/SeA strains. They were generally somewhat lower than in BALB/cHeA strain mice foster-nursed on high mammary cancer strain mice. BALB/cHeA strain milk showed some positivity for both MTV proteins at the borderline of detection (0.1 ng/mg protein). (C57BLxC3Hf)F1 hybrid mice had even less MTVp27 and gp52 in their milk than the C3Hf strain mice, permitting genetic analysis of the gene for this suppression by the C57BL genotype. These results show that the general rule that high mammary cancer strains have a high level of MTV proteins in their milk applies to the Japanese strains and that foster nursing leads to disappearance of these high levels. (24 refs)

79-6399 Reticulum Cell Neoplasms Induced in C57BL/6 Mice by Cultured Virus Grown in Stromal Hematopoietic Cell Lines. (Eng) Haas, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Meshorer, A. *J Natl Cancer Inst* 63(2): 427-439; 1979.

The isolation and properties of 31 adherent cell lines established from the spleens, lymph nodes, and bone marrow of C57BL/6 mice carrying radiation leukemia virus-induced reticulum cell neoplasms (RCN) are reported. The cell lines had a stable epithelial or fibroblastoid morphology. Supernatant virus from these lines induced splenic and lymph node RCN in 100% of inoculated C57BL/6 mice within 30 days. The disease was generalized and involved many organs. The monolayer cells themselves were not tumor cells, and they induced RCN through infection of the host with RCN virus. Simultaneous inoculation of in vitro-grown RCN-inducing virus and thymic lymphosarcoma virus induced each disease independently with no changes in incidence, latency period, and organ involvement. No mutual enhancement or inhibition was found, which indicates that two separate mechanisms of action were involved. Reextraction of the viruses from spleen, lymph nodes, and thymus gland indicated the specific organotropism of each agent. All the adherent cell lines that were derived from hematopoietic tissues produced ample potent RCN-inducing virus. This high success rate suggests that in the hematopoietic organs, the stromal fibroblastoid cells are a natural habitat for RCN-inducing virus. RCN-inducing viruses may well be synthesized in these hematopoietic stromal cells. RCN-inducing virus from culture supernatants contained high-titer infectious ecotropic and xenotropic virus that was titrated. The cultures are being used to clone the RCN-inducing virus and to establish the virologic and molecular properties that endow it with specific RCN-inducing capacity. (41 refs)

79-6400 Thermolabile Protein Kinase Molecules in a Temperature-sensitive Murine Sarcoma Virus Pseudotype. (Eng) Sen, A. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20205); Todaro, G. J.; Blair, D. G.; Robey, W. G. *Proc Natl Acad Sci USA* 76(8): 3617-3621; 1979.

Murine sarcoma virus-associated protein kinases that bind to actin have been purified by affinity chromatography on actin coupled to Sepharose. Heat inactivation studies showed the presence of thermolabile enzyme activity in pseudotypes containing a temperature-sensitive mutant of murine sarcoma virus (MSV) but not in two independent wild-type MSV pseudotypes. Studies with Sephadex G-75 column fractions showed that a low mol wt form, approx 15,000, is the major thermolabile kinase in the temperature-sensitive MSV virions. Antibodies raised against the MSV-coded

p60 protein, when added to the in vitro reaction mixtures, showed specific phosphorylation of the IgG heavy chain and a simultaneous reduction in the extent of phosphotyrosine phosphorylation catalyzed by the various MSV pseudotype kinases. Thus a transforming retrovirus-coded enzyme activity that interacts directly with a major cytoskeletal protein and whose activity parallels the transforming ability of a conditional MSV mutant was identified. (18 refs)

- 79-6401** Abelson Murine Leukemia Virus-infected Cell Lines Defective in Transformation. (Eng) Sacks, T. L. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD 20014); Hershey, E. J.; Stephenson, J. R. *Virology* 97(2): 231-240; 1979.

The isolation of two distinct classes of transformation-defective cell lines nonproductively infected with Abelson leukemia virus (AbLV) is described. One group was selected as spontaneous revertants of an AbLV-transformed mink cell line. Mutants of this group were defective both in transformation and in expression of gag gene proteins (p15 and p12) encoded by the amino terminal region of the AbLV genome. Superinfection of such cell clones by various helper viruses led to rescue of wild-type AbLV, indicating that the transformation defect in the morphologically reverted clones involves a defect in cellular genes influencing transformation rather than in the viral genome itself. Mutants of the second group were isolated by screening single cell clones, newly infected by AbLV pseudotype virus, for expression of p12 antigen in the absence of either transformation or virion production. Twenty such mutants were selected. All clones except one expressed high levels of p15 and p12 in the absence of detectable levels of other gag gene-coded structural proteins. One clone was also positive for envelope glycoprotein (gp70) apparently encoded by a replication-defective helper virus mutant. In the second group of mutant cell clones, attempts to isolate wild-type AbLV were unsuccessful. Moreover, transformation could be induced following superinfection with wild-type AbLV pseudotype virus but not with superinfection by helper virus alone. The possibility that these latter mutants may be viral rather than cellular in origin is discussed. (20 refs)

- 79-6402** Properties of DNA-dependent RNA Polymerases from Spleen of Rats Inoculated with Rauscher Leukemia Virus. (Rus) Pravdina, N. F. (D. I. Ivanovskii Inst. Virology, Moscow, USSR); Veselovskaia, T. V.; Galegov, G. A. *Biokhimiia* 44(6): 1137-1144; 1979.

This study was designed to evaluate the changes in RNA polymerase activity during leukemia development. RNA polymerase was isolated from the spleens of BALB/c mice inoculated ip with 0.25 ml of supernatant obtained after centrifugation of 10% spleen cell homogenate from mice with Rauscher viral leukemia. The spleen of intact (leukemia-free) mice contained three peaks of RNA polymerase activity which corresponded to RNA polymerases A(I), A(II), and B; all three polymerases had similar, relatively low activity. On day 3 after inoculation spleen wt increased to 200 g and the chromatographic profile and activities of polymerases were similar to those in controls. At early stages of leukemia development (day 5: spleen wt increased to 300 mg), there was a marked, twofold increase of RNA polymerase B activity. Progressive development of leukemia (increase of spleen wt to >600 mg) was associated with the increase of RNA polymerase activity and appearance of RNA polymerase C. In vitro incubation of polymerases with the semisynthetic antibiotic

dihydrorifampicin resulted in a 50% inhibition of RNA polymerase activity. (20 refs)

- 79-6403** Preparation of Syngeneic Tumor Regressor Serum Reactive with the Unique Determinants of the Abelson Murine Leukemia Virus-encoded P120 Protein at the Cell Surface. (Eng) Witte, O. N. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA 02139); Rosenberg, N.; Baltimore, D. *J Virol* 31(3): 776-784; 1979.

Syngeneic tumor regressor serum reactive with the Abelson murine leukemia virus (A-MuLV)-specified P120 (anti-AbT sera) were produced in C57L/J mice. Of many mouse strains tested, only C57L/J reproducibly rejected syngeneic A-MuLV-induced tumor cells; after multiple immunizations, their sera would immunoprecipitate both P120 and Moloney-MuLV (M-MuLV) proteins. Using labeled A-MuLV-induced nonproducer cells, only P120 could be detected using anti-AbT sera, suggesting that it may be the only A-MuLV-specified protein. Reactivity of anti-AbT sera with P120 was not blocked by M-MuLV virion proteins, implying that the sera recognize a portion of P120 that is not homologous to any M-MuLV product. Anti-AbT sera stained the surface of live A-MuLV-transformed nonproducer cells in a two-stage immunofluorescence assay, and such staining was not blocked by M-MuLV protein. Also, intact A-MuLV-transformed cells absorbed much of the reactivity of certain anti-AbT sera for P120. Thus, a portion of P120 appears to be exposed on the surface of transformed cells. P120 lacked detectable carbohydrate, was not affected by endoglycosidase H, and could not be labeled by lactoperoxidase-catalyzed iodination, indicating that it is an unusual surface protein. (32 refs)

- 79-6404** Lack of Correlation of Onset of Lymphomas and Levels of Murine Leukaemia Virus in (AKR x CBA/H-T6Crc) F1. (Eng) Barnes, R. D. (Dept. Embryology and Foetal Development, Clinical Res. Centre, Watford Rd., Harrow, Middlesex, England); Tuffrey, M.; Simpson, M. *Eur J Cancer* 15(8): 1043-1049; 1979.

The onset of lymphoma development in (AKR x CBA/H-T6Crc)F1 hybrid mice was correlated with the levels of murine leukemia virus (MuLV) in these animals. Compared with the parental AKR mice, lymphoma development was delayed in reciprocal AKR x CBA crosses. The levels of p30 were considerably lower in CBA controls than in macroscopically normal AKR controls and were significantly higher in the (CBA x AKR)F1 hybrids than in the AKR parents ($p < 0.05$). No antibody activity against AKR virus was demonstrated in any of 75 individual serum samples obtained from (AKR x CBA)F1 mice, suggesting the absence of "free" anti-AKR MuLV activity in the F1 hybrids up to 1 yr of age. The data indicate that lymphoma susceptibility is not invariably linked to the viral load in AKR-derived hybrids. (21 refs)

- 79-6405** H-2-Dependent Regulation of the High Level of Expression of Ecotropic Murine Leukemia Virus. (Eng) Colombatti, A. (Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ., 725 N. Wolfe St., Baltimore, MD 21205); Dux, A.; Berns, A.; Demant, P.; Hilgers, J. *J Natl Cancer Inst* 63(3): 869-873; 1979.

Ecotropic virus expression was examined in an H-2 congenic mouse strain on a B10 background. Adult B10.Y mice, which are congenic with C57BL/10ScSn (B10) mice for the H-2 region, expressed a high titer of infectious ecotropic virus in the spleen. B10 mice uniformly lacked detectable virus expression in the XC plaque assay or by immunofluorescence. F₁ hybrids between B10.Y and B10 mice were negative or had very low levels of virus expression. Among (B10.Y x B10)F₂ segregant mice, 11/17 virus-positive mice were H-2^{pa/pa} homozygous and 6, H-2^{pa/b} heterozygous. None of the H-2^{b/b} mice had detectable virus levels. This demonstrates that B10.Y mice possess a recessive gene within or close to the H-2 complex for the high-grade virus expression and that the H-2^b haplotype prevents the spontaneous expression of ecotropic virus in this hybrid. Molecular hybridization experiments with a selected ecotropic AK/R murine leukemia virus cyclic DNA probe indicated that both parental strains possessed ecotropic virus sequences and that the number of sequences was the same in B10.Y and B10 mice. This finding excludes the possibility that the H-2-related effect might be due to the presence of additional viral structural genes without or close to the H-2 region of B10.Y mice. The results demonstrate that genes within the H-2 region regulate the expression of endogenous viral genomes. To date, the evidence indicates that the genetic effect that results in a high level of expression of ecotropic virus early in life is also responsible for the high incidence of lymphomas in the B10.Y strain. (29 refs)

79-6406 A Murine Teratocarcinoma Stem Cell Line Carries Suppressed Oncogenic Virus Genomes. (Eng) Huebner, K. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Tsuchida, N.; Green, C.; Croce, C. M. *J Exp Med* 150(2): 392-405; 1979.

Stem cell lines and differentiated cell lines established from a murine strain 129 testicular teratocarcinoma (OTT6050) were characterized with regard to their interaction with murine leukemia virus (MuLV). The stem cell line, which was completely nonpermissive to productive infection by Moloney MuLV and consisted of 97% pluripotent stem cells, contained DNA copies of an RNA tumor virus that was indistinguishable from the N-tropic MuLV of AKR mice. The stem cells were negative for the expression of viral reverse transcriptase (RT), p30, and gp69/71, and no virus was found by the XC plaque assay or other biological tests. Differentiated cells established from the same tumor were 100% positive for viral gp69/71 and p30, and they produced large amounts of RT activity and N-tropic virus. The virus isolated from these cells was closely related, if not identical, to AKR N-tropic virus and, thus, was not an endogenous virus of strain 129 mice. The teratocarcinoma tumor from which these lines were established had been carried in strain 129 mice, and perhaps at some time in the passage history, the tumors were nonproductively infected with the N-tropic virus. The OTT6050-derived stem and differentiated cell lines should be useful in defining in stem cells the step at which ecotropic MuLV replication is blocked. (42 refs)

79-6407 The Spleen Focus-forming Virus (SFFV)-specific Neoantigen Shares Cross-reactive Determinants with Mink Cell Focus-inducing (MCF) Virus gp70. (Eng) Gillis, S. (Hematology Res. Lab., Dept. Medicine, Dartmouth-Hitchcock Medical Center, Hanover, NH 03755); Ruscetti, S. K.; Gillis, A. E.; Troxler, D. H.; Scolnick, E. M.; Smith, K. A. *Virology* 96(2): 421-428; 1979.

An attempt was made to determine whether the spleen focus-forming virus (SFFV)-specific neoantigen, as defined by in vitro

cytolysis, shared determinants with antigens coded for by mink cell focus (MCF)-inducing viruses, which, like SFFV, are also xenotropic/ecotropic recombinants. As detected by direct cytolysis of SFFV- and MCF-infected target cells, the SFFV-specific neoantigen was partially cross-reactive with determinants on the surface of MCF virus-infected cells. The cross-reactive determinants appeared to be coded for by the envelope region of both AKR and Moloney MCF viruses, in that antisera specific for MCF gp70 were capable of blocking SFFV-specific neoantigen-directed cytolysis. These results provide further evidence in support of the recombinant nature of the SFFV genome and its close relationship to MCF viral genetic information. However, in that the SFFV-specific neoantigen was not totally cross-reactive with MCF gp70, it is possible that additional antigenic determinants associated with SFFV-encoded transformation may be present. (13 refs)

79-6408 Spontaneous Regression of Friend Murine Leukemia Virus-induced Erythroleukemia. IV. Effects of Radiation and Athymia on Leukemia Regression in Mice. (Eng) Furmanski, P. (Dept. Biology, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI 48201); Dietz, M.; Fouche, S.; Hall, L.; Clymer, R.; Rich, M. A. *J Natl Cancer Inst* 63(2): 449-454; 1979.

A study was made of the effects of immunosuppressive procedures (ie, x-radiation, congenital athymia, and ⁹⁰Sr irradiation of the bone marrow) on leukemia regression in mice. The spontaneous regression of the erythroleukemia (EL) induced by the regressing Friend murine leukemia virus (F-MuLV) complex was inhibited by irradiation of the animals prior to F-MuLV inoculation. This inhibition was proportional to the radiation dose used. Treatment of the mice with the bone-seeking isotope ⁹⁰Sr also inhibited EL regression, which implicates the same effector mechanisms involved in the resistance to F-MuLV- or F-MuLV-induced immunosuppression. EL's induced in athymic nude mice by the regressing F-MuLV complex exhibited higher rates of lethality than did the leukemias in heterozygous or homozygous thymus gland-containing controls. These data suggest the involvement of the immune system in EL regression and the specific participation of thymus cells and an ⁹⁰Sr-susceptible function, perhaps marrow-dependent cells, in the process of regression. (29 refs)

79-6409 Virus Expression in Various Tissues of Mice Inoculated With Variants of Gross Leukemia Virus. (Eng) Santillana, M. (Tissue Culture and Virus Lab., E.R. No. 38, C.N.R.S., Quai Anatole-France, Paris 7e, France); Chiric, E.; Youn, J. K. *Eur J Cancer* 15(7): 953-963; 1979.

An in vitro XC coculture technique and electron microscopy were used to study the evolution of virus expression in various lymphoid tissues of C3H/Fe mice inoculated with two variants of tissue culture-adapted Gross passage A virus. When neonates were inoculated with a highly leukemogenic variant (TGV virus), three phases of virus expression could be distinguished during the latent period (av, 2 mo). In the early phase (first 3 wk after virus inoculation) as well as in the later phase (after day 50), there were abundant levels of virus in the bone marrow and spleen, moderate levels in the thymus, and slight levels or no virus in the lymph nodes and kidneys. In the intermediate phase (days 20-50), the virus disappeared completely or decreased significantly in all tissues tested. When neonates were inoculated with a nonleukemogenic variant (N1 virus), no virus could be detected in all tissues examined during the 2-mo period after virus inoculation. The virus recovered

from in vitro explanted and cultured kidney cells taken from mice inoculated with TGV virus induced typical Gross-type lymphoid leukemia in all C3HeB/Fe mice inoculated as newborns. However, the in vitro cellular tropism of this virus was B-tropic, but that of the original TGV virus was N-tropic. Frequent differentiation to heterologous tissues was observed electron microscopically in the thymuses of mice inoculated with TGV virus. (18 refs)

- 79-6410** Molecular Cloning of the Harvey Sarcoma Virus Closed Circular DNA Intermediates: Initial Structural and Biological Characterization. (Eng) Hager, G. L. (Tumor Virus Genetics Branch, NCI, Bethesda, MD 20205); Chang, E. H.; Chan, H. W.; Garon, C. F.; Israel, M. A.; Martin, M. A.; Scolnick, E. M.; Lowy, D. R. *J Virol* 31(3): 795-809; 1979.

The circular forms of Harvey sarcoma virus (HaSV) DNA inserted in the λ gtWES.1B vector and cloned in an approved EK2 host were characterized by restriction endonuclease digestion, molecular hybridization, electron microscopy, and infectivity. Four of the six HaSV DNA inserts were identical, containing about 6.0 kilobase pairs (kbp) and comigrating in agarose gels with the infectious, unintegrated, linear HaSV DNA. One insert was approx 0.65 kbp smaller and one was approx 0.65 kbp larger than these four inserts. R-looping with HaSV RNA revealed that the smallest insert contained one copy of the HaSV RNA. Preliminary restriction endonuclease digestion of the recombinant DNAs suggested that the middle-sized inserts contained a 0.65-kbp duplication of sequences present only once in the smallest insert. This duplication corresponded to the 0.65-kbp terminal duplication of the unintegrated linear HaSV DNA. The largest insert apparently contained a tandem triplication of these terminally located sequences. DNA of all three sized inserts induced foci in NIH 3T3 cells, and focus-forming activity could be rescued from the transformed cells by superinfection with helper virus. Infectivity followed single-hit kinetics, suggesting that the foci were induced by a single molecule. (42 refs)

- 79-6411** Identification of a Sarcoma Virus-coded Phosphoprotein in Nonproducer Cells Transformed by Kirsten or Harvey Murine Sarcoma Virus. (Eng) Shih, T. Y. (Lab. Tumor Virus Genetics, NCI, NIH, Bethesda, MD 20205); Weeks, M. O.; Young, H. A.; Scolnick, E. M. *Virology* 96(1): 64-79; 1979.

A 21,000-dalton protein (p21) coded for by Harvey or Kirsten murine sarcoma virus (Ha- or Ki-MuSV) was identified in non-producer cells transformed by these two viruses. Antisera prepared from rats bearing tumors induced by syngeneic transplantation of normal rat kidney cells transformed by Ha-MuSV specifically precipitated the Ha-MuSV p21 from a nonproducer BALB/c mouse cell and a nonproducer dog cell transformed by Ha-MuSV. The same antisera also precipitated a similar protein, Ki-MuSV p21, from a nonproducer mink cell transformed by Ki-MuSV. Both p21's were phosphoproteins. Previous studies have reported the production of a virus-specific p21 polypeptide from the translation of Ha-MuSV RNA in cell-free protein synthesis systems. This p21 protein was specifically precipitated by the same antitumor sera. Similarly, a p21 polypeptide translated from Ki-MuSV RNA was also specifically precipitated by the antitumor sera. Therefore, it is concluded that the p21 of Ha-MuSV and Ki-MuSV are homologous proteins coded for by homologous sequences found in the recombinant genomes of Ha-MuSV and Ki-MuSV. (31 refs)

- 79-6412** Inhibition of Spontaneous Transformation of Rat Embryo Cells Releasing Endogenous Type C Virus by Virus-Specific Antiserum. (Eng) Rasheed, S. (Dept. Pathology, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033); Young, H.; Gardner, M. B. *J Natl Cancer Inst* 63(3): 745-750; 1979.

Three clonal Sprague-Dawley (SD-1) cell lines, each releasing endogenous rat leukemia virus (RaLV), were treated with RaLV-specific antiserum (1:250 dilution) for 3, 7, or 15 days. Following this treatment, transformation was delayed 6-28 wk after control SD cultures had transformed. Transformation of SD-1 cell clones in the absence of RaLV antiserum was a highly reproducible and predictable event. Treatment with RaLV-specific antiserum also reduced virus production and infectivity. Transformation in the SD-1 cell system was not correlated with increasing levels of Kirsten murine sarcoma virus-related *src* RNA because similar amounts of these transcripts were detected in both transformed and nontransformed (RaLV-antiserum-treated) cell clones. However, the non-transformed SD-1 cells contained 10-fold lower levels of RaLV-related RNA than did the transformed cells. These results indicate that a minimum threshold of infectious virus expression is required for transformation to occur. (18 refs)

- 79-6413** Moloney Murine Sarcoma Virions Synthesize Full-Genome-Length Double-stranded DNA In Vitro. (Eng) Benz, E. W. (Dept. Developmental Biology and Cancer, Albert Einstein Coll. Medicine, Bronx, NY 10461); Dina, D. *Proc Natl Acad Sci USA* 76(7): 3294-3298; 1979.

The in vitro synthesis of full-length viral double-stranded DNA by moloney murine sarcoma virus (MSV) virions disrupted by Triton X-100 is described. The major product, a 5,950-base pair (6-kilobase pair DNA) double-stranded DNA, was characterized by cleavage with restriction endonucleases and shown to contain a 600-nucleotide-long direct repeat at both ends of the MSV genome. Linear DNA molecules made in vivo shortly after infection were compared with the linear double-stranded DNA synthesized in vitro. The restriction maps of both viral DNA products were indistinguishable. The 600-base pair repeat resulted in a progeny DNA molecule that was longer than the parental MSV genomic RNA. The generation of this repeat must involve a mechanism that allows the viral reverse transcriptase (RNA-dependent DNA nucleotidyltransferase) to copy 5'- and 3'-terminal genomic (+) strand sequences twice. (27 refs)

- 79-6414** Heat-labile Character of Murine Sarcoma-Xenotropic Leukemia Virus Complex in Duck Cells. (Eng) Hirai, R. (Tokyo Metropolitan Inst. Medical Science, Honkomagome, Bunkyo-ku, Tokyo 113, Japan); Yuasa, Y.; Yamamoto, T. *Virology* 96(2): 615-621; 1979.

The infection of duck embryo (DE) cells with the xenotropic murine leukemia virus (X-MuLV) pseudotype of wild-type Moloney murine sarcoma virus (MSV) was investigated. The MSV(X-MuLV) complex induced foci and replicated in DE cells at 37 C. Both Japanese quail and chick embryo cells were resistant to infection with MSV(X-MuLV). At 41 C, the number of foci induced by MSV(X-MuLV) in DE cells was one-hundredth that induced at 37 C. In contrast, avian sarcoma virus (ASV) subgroup C transformed DE cells with almost equal efficiency at 37 and 41 C. The temperature-sensitive step of MSV(X-MuLV) resided in the early phase of infection (within 24 hr postinfection). MSV(X-

MuLV) virions were more heat-labile than ASV virions and phenotypically mixed ASV virions with X-MuLV properties. The virion-associated reverse transcriptase activity of X-MuLV was rapidly inactivated at 41 C, but the enzyme activity of ASV was stable at 41 C. The results suggest that the reduction of infectivity of MSV(X-MuLV) in DE cells at 41 C is due to the heat-labile character of the reverse transcriptase of X-MuLV. (26 refs)

- 79-6415 Heteroduplex Analysis of the Sequence Relationships Between the Genomes of Kirsten and Harvey Sarcoma Viruses, Their Respective Parental Murine Leukemia Viruses, and the Rat Endogenous 30S RNA. (Eng) Chien, Y. H. (Dept. Chemistry and Chemical Engineering, California Inst. Technology, Pasadena, CA 91125); Lai, M.; Shih, T. Y.; Verma, I. M.; Scolnick, E. M.; Roy-Burman, P.; Davidson, N. *J Virol* 31(3): 752-760; 1979.

The sequence relationships between Kirsten murine sarcoma virus (Ki-SV), Harvey murine sarcoma virus (Ha-SV), and a rat endogenous 30S RNA were studied by electron microscope heteroduplex analysis, as were the sequence relationships between the sarcoma viruses and their respective parental murine leukemia viruses (Kirsten and Moloney murine leukemia viruses) and between the two murine leukemia viruses themselves. The only observed nonhomology feature of the Kirsten murine leukemia virus/Moloney murine leukemia virus heteroduplexes was a substitution loop with two arms of equal length extending from 1.80 ± 0.18 kilobases (kb) to 2.65 ± 0.27 kb from the 3' end of the RNA. It is believed that this feature lies in the *env* gene region of the viral genomes. The Ha-SV and Moloney murine leukemia virus genomes (respective lengths, 6.0 and 9.0 kb) were homologous only in a 1.0 ± 0.05 -kb region at the 3' end and possibly over a 200-nucleotide region at the 5' ends. Ha-SV and Ki-SV (length, 7.5 kb) were homologous in the first 4.36 ± 0.37 -kb region from the 3' end and in a 0.70 ± 0.15 -kb-region at the 5' end. In between, there was a generally nonhomologous region, possibly containing a short (0.23-kb) region of partial or total homology. Rat endogenous 30S RNA and Ki-SV showed mixed regions of sequence homology and nonhomology at both the 5' and 3' ends. However, there was a large (4-kb) region of homology between Ki-SV and the rat 30S RNA in the center of the genomes, with only a small nonhomologous hairpin feature. The regions of homology between the Ha-SV and Ki-SV genomes and between these viruses and the rat endogenous 30S RNA may be related to the oncogenicity of the viruses. In particular, the 0.7-kb region of homology of Ha-SV with Ki-SV at the 5' ends may be related to the formation of a 21,000-dalton phosphoprotein in cells transformed by either virus. (20 refs)

- 79-6416 Mutant of B-Tropic Murine Leukemia Virus Synthesizing an Altered Polymerase Molecule. (Eng) Gerwin, B. I. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20205); Rein, A.; Levin, J. G.; Bassin, R. H.; Benjers, B. M.; Kashmiri, S. V.; Hopkins, D.; O'Neill, B. J. *J Virol* 31(3): 741-751; 1979.

A nonconditional mutant of B-tropic murine leukemia virus (MuLV), defective in polymerase, was isolated by cloning chronically infected cells. The mutant-containing clone produced virus particles which were noninfectious. However, superinfection of the cells by replication-competent XC-negative viruses resulted in the rescue of virus capable of forming plaques in a modified XC test, termed the "complementation plaque assay". Analysis of the

noninfectious virions produced without superinfection demonstrated that they contained only 2 to 5% of the wild-type level of reverse transcriptase activity. Purification of this activity indicated that it was associated with a smaller molecule than that produced by wild-type virus. Cells producing the mutant virions did not contain the *gag-pol* precursor Pr180-^{gag-pol}, but did contain proteins of 147K and 114K daltons precipitable with anti-*pol* serum. All of the normal structural proteins as well as 70S genomic RNA could be detected in the mutant particles. An interference test indicated that a functional ecotropic glycoprotein was synthesized by the mutant. These results indicate that the mutant has a unique defect in the *pol* gene. (43 refs)

- 79-6417 Studies on the DNA of an Oncogenic Papovavirus of the Syrian Hamster. (Eng) Scherneck, S. (Dept. Bioregulation, Central Inst. Molecular Biology, 1115 Berlin-Buch, E. Germany); Bottger, M.; Feunteun, J. *Virology* 96(1): 100-107; 1979.

The DNA of Syrian hamster papovavirus (HaPV) was characterized by physicochemical methods and by digestion with site-specific restriction endonucleases. The HaPV isolated from multiple skin tumors of Syrian hamsters contained supercoiled, double-stranded DNA with a guanine/cytosine content of 39.2% and a mol wt that was within the range of that of simian virus 40 (SV 40) and polyoma virus DNA. Spectrophotometric melting and annealing curves indicated a high thermal stability and a high sequence homogeneity of the HaPV DNA. Cleavage of the DNA with restriction endonucleases *Bam*H1, *Hind*II, and *Eco*RI produced one, three, and four fragments, respectively, and the electrophoretic pattern of the products of digestion was distinctly different from that of SV40 and all other known papovaviruses. The relative positions of the *Bam*H1, *Hind*II, and *Eco*RI restriction endonuclease sites were established, taking the unique *Bam*H1 site as a zero point. (17 refs)

- 79-6418 Replication of Vesicular Stomatitis Virus Facilitated by Shope Fibroma Virus In Vivo. (Eng) Crouch, N. A. (Dept. Biomedical Sciences, Rockford Sch. Medicine, Univ. Illinois Coll. Medicine, Rockford, IL 61101); Mitchell, R. L. *Infect Immun* 25(1): 213-219; 1979.

The possibility that Shope fibroma virus and vesicular stomatitis virus (VSV) can interact in vivo was examined. Rabbits inoculated id with both viruses together, or each separately, were examined for the formation of lesions or tumors and for the production of infectious virus. The presence of VSV interfered with tumorigenesis by Shope fibroma virus. Production of infectious VSV was greater in the tumors that formed than in normal skin. Hence, each virus affected the other. Sera and tissues of normal rabbits contained a substance that inhibited VSV; this substance may act to limit replication of VSV in rabbit skin. In addition, cultured rabbit skin cells appeared to adsorb VSV inefficiently. When persistently infected by Shope fibroma virus, however, adsorption of VSV was markedly improved. The results suggest that, in vivo, Shope fibroma virus may facilitate the adsorption of VSV to reduce the effect of a natural inhibitor and, consequently, enhance the production of infectious virus. (10 refs)

- 79-6419 Pathogenesis of Experimental Feline Leukemia Virus Infection. (Eng) Rojko, J. L. (Dept. Veterinary

Pathobiology, Ohio State Univ., 1925 Coffey Rd., Columbus, OH 43210; Hoover, E. A.; Mathes, L. E.; Olsen, R. G.; Schaller, J. P. *J Natl Cancer Inst* 63(3): 759-768; 1979.

Early events in the pathogenesis of feline leukemia virus (FeLV) infection were studied in 59 specific-pathogen-free cats. Young cats (≤ 8 wk old and highly susceptible to FeLV) and adult cats (> 6 mo old and relatively resistant to FeLV) were exposed to FeLV by oral-nasal, ip, or sc inoculation. The sequential distribution of FeLV group-specific antigen (GSA) in blood and tissues of susceptible vs resistant cats was correlated with alterations in hematologic and serologic parameters. Six sequential phases of FeLV infection (ie, viral replication) were identified: (1) lymphoreticular cells in local lymphoid tissues [2-4 days after exposure (DAE)]; (2) circulating lymphocytes and monocytes (early cell-associated viremia; 1-14 DAE); (3) lymphoid germinal cells in lymphoid tissues throughout the body (3-12 DAE); (4) bone marrow neutrophil and platelet precursor cells and intestinal crypt epithelium (7-21 DAE); (5) circulating neutrophils and platelets (with establishment of viremia) (≥ 14 -28 DAE); and (6) mucosal and glandular epithelial tissues (with excretion of FeLV; ≥ 28 -56 DAE). Early lymphoreticular virus replication (phases 1-3) was present in both progressive and transient infection. In cats that became persistently infected (80% of young cats and 14% of adult cats), FeLV infection was not contained in the initial lymphoreticular phases 1-3, and extensive virus replication occurred in the germinal cell populations of lymphoid, hematopoietic, and epithelial tissues (phases 3-6). In cats with progressive infections, lymphopenia and neutropenia (21-56 DAE) were associated with the appearance of FeLV GSA in circulating neutrophils and platelets (≥ 14 -28 DAE). In cats with self-limiting infections, virus containment in phases 3 or 4 correlated with transient lymphopenia (7-14 DAE) and development of antibody to the feline oncornavirus-associated cell membrane antigen. (47 refs)

79-6420 Partial Characterization of a New Type of Bovine Papilloma Viruses. (Eng) Pfister, H. (Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany); Linz, U.; Gissmann, L.; Huchthausen, B.; Hoffmann, D.; zur Hausen, H. *Virology* 96(1): 1-8; 1979.

Bovine papilloma virus (BPV) isolates from 13 individual bovine cutaneous warts were characterized by monospecific rabbit antisera. They fell into two groups without detectable crossreactivity when tested by immune electron microscopy or complement fixation. Complementary RNA transcribed from representatives of both groups did not hybridize with DNA from heterologous isolates. The two types of BPV also differed in the electrophoretic mobility of their proteins and in the mol wt of their DNA (4.5×10^6 and 4.9×10^6 daltons, respectively). One isolate with a DNA of 4.9×10^6 daltons and one isolate with a DNA of 4.5×10^6 daltons were analyzed by cleavage of their DNA with the restriction endonucleases *Bam*HI, *Eco*RI, *Hind*II, *Hind*III, and *Hae*III, and physical maps were established. The two genomes differed completely in their cleavage pattern. The *Hind*II cleavage pattern demonstrated the identity of the large DNA isolate with BPV type 2, which was recently characterized by restriction endonuclease cleavage and kinetic nucleic acid hybridization. The other apparently new type of BPV, which has been detected twice thus far, is tentatively designated as BPV type 3. (22 refs)

79-6421 The *Bevi* Locus (Chromosome 6) Encodes a Post-penetrational Cellular Function Required for Baboon Endogenous Virus Replication in Human Cells. (Eng) Lemons, R.

S. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD); O'Brien, S. J.; Sherr, C. J. *Cytogenet Cell Genet* 22(1-6): 255-259; 1978.

The genetic characteristics of a chromosome (CS) locus (*Bevi*, for baboon endogenous virus infection) on human CS 6 that positively controls baboon virus replication were studied. M7 baboon virus-infected hybrid cells were obtained by the fusion of mouse A1-2 cells (HPRT-) with six fresh human bone marrow specimens and WI38 fibroblasts and of Chinese hamster E36 cells (HPRT-) with two of the bone marrow specimens. Virus was detected in permissive cells within 3 wk after infection. Biological and immunological tests confirmed that it was distinct from murine leukemia virus (MuLV) and indistinguishable from M7. The host range of the recovered virus was identical to that of baboon endogenous virus, and group-specific anti-p30 sera yielded radioimmune precipitation curves identical to those for M7 p30 and distinct from those for Rauscher MuLV p30. Of 194 hybrid clones examined, 97% showed concordance between M7 replication and human CS 6; 39% were discordant with CS 19. These data exclude the specific participation of genes on CS 19 in baboon virus replication in human x rodent hybrids. In additional studies, human vA-2 cells (HPRT-) were infected with M7, cloned, and fused to Syrian hamster BHK-B1 cells (TK-). Again, a high concordance between human CS 6 and continued viral expression was demonstrated. Since the human parent was productively infected with M7 prior to fusion, the concordance of virus production, p30 synthesis, and CS 6 markers demonstrates that the *Bevi* locus function is subsequent to virus penetration but prior to viral protein synthesis. Preliminary molecular hybridization experiments showed that *Bevi* is the preferred integration site of baboon C-type DNA provirus in the human genome. (9 refs)

79-6422 Assignment of a Gene Required for Infection with Endogenous Baboon Virus to Human Chromosome 19. (Eng) Brown, S. (NCI-VA Oncology Branch, VA Hosp., Washington, DC); Oie, H.; Francke, U.; Gazdar, A. F.; Minna, J. D. *Cytogenet Cell Genet* 22(1-6): 239-242; 1978.

A parasexual approach using 29 independent primary human x hamster hybrid clones segregating human chromosomes was used to identify human genes required to support the replication of M7 baboon virus. Fresh human bone marrow cells from two sources were fused with Chinese hamster E36 cells, and clones were tested for susceptibility to M7 virus by a specific fluorescent antibody test that detects viral p30 protein in fixed cell preparations and by a reverse transcriptase assay. Using a modified Giemsa-trypsin banding technique, human and hamster chromosomes were identified in eight primary clones. Chromosomes 15 and 19 correlated most closely with virus replication. Each chromosome had only one discordant clone out of eight clones tested. The exceptional clone, which was virus-replication-positive without a recognizable chromosome 19, contained small fragments possibly derived from a 19. Three clones with intact chromosome 6's were unable to support infection, but one clone that supported infection had no recognizable chromosome 6. Enzyme and chromosome analyses revealed that human chromosome 19 was required for viral infection. It is not known whether the inconsistent results found with chromosome 6 represent human polymorphism or whether they indicate the existence of several genes for integration or receptor sites. (10 refs)

79-6423 Structural Analysis of the Genomes of Gibbon Ape and Woolly Monkey Leukosis Viruses. (Eng)

Sahagan, B. G. (Sidney Farber Cancer Inst., Boston, MA 02115); Haseltine, W. A. *J Virol* 31(3): 657-667; 1979.

The RNAs of gibbon ape and woolly monkey leukemia viruses were compared by two-dimensional polyacrylamide gel electrophoresis of the large RNase T1-resistant oligonucleotides. Polyadenylic acid-containing 70S genomic RNA was isolated from purified virions and fingerprinted. The fingerprints of two gibbon ape viruses (GaLV-H and GaLV-Br) were very similar, the majority of the oligonucleotides of these two viruses having the same electrophoretic mobility. Electrophoresis of 14 pairs of RNase T1-resistant oligonucleotides indicated that most such oligonucleotides that comigrated probably had the same sequences. The other viruses studied (simian sarcoma-associated virus, gibbon ape leukemia virus-Thailand, and gibbon ape leukemia virus-San Francisco) showed an extensive but somewhat lower degree of sequence identity (between 40% and 60% of the genomes). (28 refs)

79-6424 Establishment of a Lymphoblastoid Cell Line and Isolation of an Epstein-Barr-related Virus of Gorilla Origin. (Eng) Neubauer, R. H. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Rabin, H.; Strnad, B. C.; Nonoyama, M.; Nelson-Rees, W. A. *J Virol* 31(3): 845-848; 1979.

An antigenically unique virus (Herpesvirus gorilla, HVG) isolated from cultured mononuclear cells (Machi cells) of the peripheral blood of a female gorilla (*Gorilla gorilla*) was characterized. The Machi cells contained surface IgG and released IgG, were positive for Fc receptors and negative for sheep RBC receptors, and were therefore considered to be of B-cell origin. Approx 1%-2% of the cells were positive for antibodies related to Epstein-Barr virus (EBV). The early antigen of EBV and HVG differed in some respects, however, as did the nuclear antigen of HVG, Herpesvirus papio, and EBV. HVG DNA hybridized 30%-40% to EBV DNA and was present in Machi cells at approx 40-50 genome copies/cell. Cells from two gibbons inoculated with Machi culture fluids showed signs of transformation within 14 days and gave rise to two lymphoid cell lines. Machi cells also showed a low level of positivity for type C RNA virus. (18 refs)

79-6425 Methylation of *Herpesvirus saimiri* DNA in Lymphoid Tumor Cell Lines. (Eng) Desrosiers, R. C. (New England Regional Res. Center, Harvard Medical Sch., One Pine Hill Drive, Southborough, MA 01772); Mulder, C.; Fleckenstein, B. *Proc Natl Acad Sci USA* 76(8): 3839-3843; 1979.

Several continuous lymphoid cell lines have been established from tumors induced by *Herpesvirus saimiri*. At least a portion of the viral DNA in the marmoset lymphoid cell line 1670, which does not produce detectable virus, is present as covalently closed circular episomal DNA. The use of restriction endonuclease digestion, transfer to nitrocellulose filters, and hybridization of the virus-specific DNA produced strong evidence that viral DNA sequences present in total 1670 cell DNA and in isolated episomes are extensively methylated. The restriction endonuclease *Hpa* II has the same recognition sequence as *Msp* I but, unlike *Msp* I, failed to cleave when the C of the C-G dinucleotide was methylated. Viral DNA sequences of 1670 cells were refractory to cleavage by *Hpa* II but not *Msp* I; greater than 80% of the *Hpa* II cleavage sites appeared to be methylated. Similarly, viral DNA sequences of 1670 cells were refractory to cleavage by *Sma* I (C-C-C-G-G-G)

and *Sac* II (C-C-G-C-C-G) but not *Sac* I, *Pvu* II, or *Pst* I, which lacked the dinucleotide C-G in their recognition sequences. Methylation of mammalian DNA has been previously found exclusively at C residues in the dinucleotide C-G. *H. saimiri* DNA sequences of another nonproducer cell line, 70N2, also appeared to be extensively methylated, but analysis of total cell DNA extracted from three virus-producing lymphoid lines revealed no evidence of methylation of viral DNA sequences. It remains to be seen if methylation of viral DNA plays a role in the lack of complete expression of *H. saimiri* genome information in nonproducing lymphoid cell lines. (22 refs)

79-6426 Association of Herpes Simplex Virus (HSV) with Cervical Cancer by Lymphocyte Reactivity with HSV-1 and HSV-2 Antigens. (Eng) Smith, J. W. (Dept. Microbiology, Louisiana State Univ. Medical Center, 1542 Tulane Ave., New Orleans, LA 70112); Torres, J. E.; Holmquist, N. D. *Am J Epidemiol* 110(2): 141-147; 1979.

Procedures for distinguishing subjects with previous herpes simplex virus (HSV)-1 and -2 infections by means of differences in lymphocyte reactivity to HSV-1 and HSV-2 antigens were developed and applied to the detection of past HSV-2 infection in 26 patients with invasive epidermoid cervical carcinoma and 26 controls matched for age, race, and socioeconomic class. In addition, lymphocyte blastogenesis (³H-thymidine uptake after 6 days incubation) induced by HSV-1 and HSV-2 antigens in persons with histories of HSV infection (11 with HSV-1, 11 with HSV-2, 16 with HSV-1 and -2, and 6 seronegative controls) was determined; lymphocytes from subjects with previous HSV-1 or HSV-2 infection had higher blastogenic responses to homologous virus antigen than to heterologous antigen. When the responses to HSV-2 were divided by the responses to HSV-1, the group with HSV-1 infection was significantly different from the HSV-2 group ($p < 0.005$), yielding a mean value of 28 compared with 132 from the HSV-2 group. Those exposed to both viruses had a value intermediate between those of the HSV-1 and HSV-2 groups. Lymphocyte populations from subjects seropositive for HSV were cross-reactive in all cases. These data suggest that the characteristic of cross-reactivity with antisera to HSV-1 and HSV-2 also occurs with cellular immune responses to viral antigens. Blood specimens were obtained from cancer patients prior to radiation therapy and separated into subpopulations by Ficoll-Hypaque centrifugation. Lymphocytes were cultured with autologous plasma and exposed to phytohemagglutinin (PHA), HSV-1, HSV-2, and control antigens. Stimulation ratios for blastogenic responses to HSV antigens and PHA were higher in cancer patients than controls. When blastogenic responses in the groups with known HSV infection were used to define ranges of HSV-2/HSV-1 ratios suggestive of previous HSV-2 infection in the cancer patients, up to 88% of cancer patients were found to have suffered previous HSV-2 infection, whereas <50% of controls had evidence of cellular immunity to HSV-2 ($p < 0.005$). When the same criteria were applied to analyses of lymphocytes from subjects who had had previous infection with both HSV-1 and HSV-2, past infection with HSV-2 was not detected in all cases, suggesting that dual infection may modify the blastogenic response to a degree sufficient to mask evidence of immunity to HSV-2. (16 refs)

79-6427 Regulation of Persistent Infection with Herpes Simplex Virus In Vitro by Hydrocortisone. (Eng) Nishiyama, Y. (Dept. Microbiology and Specialized Cancer Res. Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Rapp, F. *J Virol* 31(3): 841-844; 1979.

About 1% of Raji cells showed sensitivity to herpes simplex virus type 2 (HSV-2) infection when tested by infectious center assays or immunofluorescence tests, and the percentage did not change during cell passage. The addition of hydrocortisone to Raji cells persistently infected with HSV-2 caused a marked increase in virus production and in the number of HSV-producing cells. In the case of HSV-1, the addition of hydrocortisone was required to maintain persistent infection. These observations suggest that control of replication of HSV-1 and HSV-2 in these cells is regulated by different mechanisms. (12 refs)

- 79-6428 Biological and Biochemical Observations on Isolates of EB Virus from the Malignant Epithelial Cells of Two Nasopharyngeal Carcinomas. (Eng) Crawford, D. H. (Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England); Epstein, M. A.; Bornkamm, G. W.; Achong, B. G.; Finerty, S.; Thompson, J. L. *Int J Cancer* 24(3): 294-302; 1979.

The behavior and biochemical nature of Epstein-Barr (EB) virus isolated from tumors of two separate nasopharyngeal carcinomas passaged in nude mice (NPC) were investigated. Fetal mononuclear cells infected with cyst fluid from nude-mouse-grown NPC proliferated into a cell line after 20 days in culture. Adult seronegative mononuclear cells also produced a cell line (J-ABA) after 40 days in coculture with nude-mouse-grown NPC fragments. Marmoset mononuclear cells cocultivated with x-irradiated J-ABA cells grew into a cell line after 47 days. Chromosome analysis indicated that the target cells had been transformed in each case, and immunofluorescence showed that each line contained >90% EB nuclear antigen (NA)-positive cells. The lymphoblastoid nature of all the cell lines was confirmed by light and electron microscopy. The fetal-derived lines did not produce virus spontaneously, could not be activated with various inducers, and carried only small numbers of genome copies per cell. Electron microscopy showed that the J-ABA and the marmoset lines produced C-type retrovirus particles and could be induced to produce more virus by treatment with 5-iododeoxyuridine or 12-O-tetradecanoylphorbol-13-acetate. These findings demonstrate that the incidence of productively infected cells in these lines is not determined by the intrinsic capabilities of the NPC-derived virus they carry but by the target cell from which the line originates. (52 refs)

- 79-6429 Production of Lymphoid Tumors in Hamsters by Direct Implantation of Human Umbilical Cord WBC. I. Production of Lymphoid Tumors and Their Culture and Serial Transplantation. (Jpn) Matsuda, Y. (Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan). *Acta Haematol Jpn* 42(3): 357-367; 1979.

Lymphoid tumors were produced in antilymphocyte serum-treated newborn Syrian hamsters that were given intraarterial transplants of human umbilical cord leukocytes (HCL) infected or noninfected with Epstein-Barr virus. Human lymphoblastoid cell lines were cultured from the lymphoid tumors and the tumors were transplanted serially. Lymphoid tumors were discovered by autopsy 10-27 days after administration of EBV-infected HCL in 25/25 hamsters and in 24/33 hamsters after administration of noninfected HCL. Histological examination showed lymphosarcoma-like lymph node enlargement and malignant cell infiltration of the organs. EBV-positive human lymphoblastoid cell lines were established from EBV-infected HCL-induced tumors, but not

from noninfected HCL-induced tumors. However, infection of the latter with EBV at culture initiation resulted in the establishment of EBV-positive human lymphoblastoid cell lines. These lines had a human diploid karyotype. The tumor cells were transplanted for two passages in newborn hamsters. The results indicate that EBV infection is not a prerequisite for the in vivo production of lymphoid tumors but that it is necessary for the in vitro establishment of lymphoblastoid cell lines from these tumors. The graft-vs-host reaction may have a role in the production of tumors in this experimental model. (24 refs)

- 79-6430 Epstein-Barr Virus DNA Is Amplified in Transformed Lymphocytes. (Eng) Sugden, B. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Phelps, M.; Domoradzki, J. *J Virol* 31(3): 590-595; 1979.

Leukocytes isolated from two adult donors who lacked detectable antibodies to Epstein-Barr virus-associated antigens were exposed to an av of 0.02 to 0.1 DNA-containing particles of Epstein-Barr virus per cell and immediately cloned in agarose. Within about 30 generations all transformed cell clones contained between 5 and 800 copies of viral DNA per cell. Only 1 in 10^4 to less than 1 in 10^5 of the cells of each clone released virus, and the frequency of release was not correlated with the av number of copies of viral DNA per cell. When one clone with an av of 5 copies of viral DNA per cell was recloned, the av number of copies in 4 of 6 subclones increased 15- to 50-fold while the subclones were being propagated sufficiently for study. These results indicate that Epstein-Barr virus DNA can undergo amplification relative to cell DNA at different times after it transforms cells. (18 refs)

- 79-6431 Analysis of Early and Late Epstein-Barr Virus Associated Polypeptides by Immunoprecipitation. (Eng) Mueller-Lantzsch, N. (Institut für Virologie, Zentrum für Hygiene der Universität Freiburg, Hermann-Herder-Strasse 11, D-7800 Freiburg, W. Germany); Yamamoto, N.; zur Hausen, H. *Virology* 97(2): 378-387; 1979.

The Epstein-Barr virus-producing cell lines P3HR-1 and B95-8 and the nonproducer cell lines Raji clone No. 7 and NC37 were induced to viral antigen synthesis by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) and then analyzed by immunoprecipitation with human sera for early and late virus-associated polypeptides. After labeling of producer cells for a 4-day period with [35 S]methionine, two polypeptides with mol wt of 140,000 and 150,000 were identified, reacting predominantly with virus capsid antigen (VCA+) sera. Analysis of purified Epstein-Barr virus demonstrated that the 140,000 polypeptide presumably represents an envelope protein while the 150,000 polypeptide is a nucleocapsid protein. In 4-hr radioactively labeled producer cells, an additional polypeptide with a mol wt of 130,000 was immunoreactive with VCA+ sera. Immunoprecipitation of [35 S]methionine-labeled cell extracts from nonproducer cells resulted in the specific precipitation of two polypeptides (mol wt 85,000 and 35,000) which most likely represent early EBV-associated proteins. Producer cells exhibited three additional apparent early EBV-associated polypeptides (mol wt 120,000, 18,000 and 16,000). None of these polypeptides could be detected in EBV genome-negative Ramos cells after TPA treatment. (36 refs)

- 79-6432 Enhancement of Epstein-Barr Virus Replication in Producer Cell Lines by a Combination of Low

Temperature and Corticosteroids. (Eng) Magrath, I. T. (Section Infectious Disease, Pediatric Oncology Branch, NCI, Bldg. 10, Rm 2B-50, Bethesda, MD 20205); Pizzo, P. A.; Novikovs, L.; Levine, A. S. *Virology* 97(2): 477-481; 1979.

The effect of a combination of low temperature and corticosteroids on virus production was examined in three Epstein-Barr virus (EBV) producer cell lines. Mycoplasma-free P3HR1, B95-8, and AG-876 cells were cultured at 32 C in the presence or absence of either dexamethasone sodium phosphate or hydrocortisone sodium succinate in concentrations between 2.5×10^{-7} and 2.5×10^{-3} mM. EBV capsid antigen (VCA) was assayed by an immunofluorescent technique. Corticosteroid-stimulated P3HR1 cells grown at 32 C showed a marked increase in the fraction of cells expressing VCA (70%-90%) compared with that in unstimulated cultures (20%-35%), but this effect was very small at 37 C. Electron microscopy of P3HR1 cell pellets showed a comparable difference in the fraction of virus-containing cells at 32 C. The av number of virions per cell was increased up to 30-fold by steroids. This phenomenon was not seen in B95-8 or AG-876 cells. In DNA quantitation studies, a typical control culture yielded 0.33 $\mu\text{g/liter}$ of pure EBV DNA, while cultures optimally stimulated with corticosteroids yielded 3.2 $\mu\text{g/liter}$ of viral DNA. In another experiment, Raji cells were exposed for 1 hr at 37 C to P3HR1 culture supernatants and were examined at 48 hr by immunofluorescence for the appearance of early antigen. The results confirmed an increase in infectious virus in steroid-treated cultures. (33 refs)

79-6433 New Classes of Viable Deletion Mutants in the Early Region of Polyoma Virus. (Eng) Griffin, B. E. (Imperial Cancer Res. Fund, London WC2, England); Maddock, C. *J Virol* 31(3): 645-656; 1979.

Viable mutants of polyoma virus which have deletions in defined parts of the early region of the genome were isolated. One class of mutants has deletions (less than 1% of viral genome length) located between 71.5 and 73.5 on the physical map of polyoma virus DNA, near the origin of replication. These mutants appear to grow and to transform cells in a manner indistinguishable from wild-type virus. A second type of mutant with deletions (about 2% of viral genome length) located between about 88 and 94.5 units on the physical map of polyoma virus DNA have altered transformation properties. One of these (which maps between 88 and 91.5 units) also has altered growth characteristics, whereas another (which maps between 91.5 and 94.5 units) resembles wild-type virus in its growth properties. The regions with deleted sequences were defined by cleaving mutant DNAs with restriction endonucleases and analyzing pyrimidine tracts. (35 refs)

79-6434 Molecular Cloning of Polyoma Virus DNA in *Escherichia coli*: Oncogenicity Testing in Hamsters. (Eng) Israel, M. A. (Recombinant DNA Res. Unit, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD 20205); Chan, H. W.; Martin, M. A.; Rowe, W. P. *Science* 205(4411): 1140-1142; 1979.

Inoculation of suckling hamsters with 2×10^8 live cells of *Escherichia coli* K12 strain χ 1776, carrying the complete genome of polyoma virus in a recombinant plasmid, failed to induce tumors in any of 32 recipients. Lambda phage DNA and particles with a monomeric insert of polyoma DNA also did not induce tumors. Purified recombinant plasmid DNA, as well as phage par-

ticles and DNA containing a head-to-tail dimer of polyoma DNA, showed a low degree of oncogenicity, comparable to that of polyoma DNA prepared from mouse cells. These findings support the previous conclusions, based on infectivity assays in mice, that propagation of polyoma virus DNA as a component of recombinant DNA molecules in *E. coli* reduces its biologic activity by many orders of magnitude relative to the virus itself. (10 refs)

79-6435 Cell Cycle Dependence of Transformation Expression in Mouse Cells Transformed by a Thermosensitive Mutant (Ts-121) of Polyoma Virus. (Eng) Okada, Y. S. (Natl. Inst. Radiological Sciences, Anagawa, Chiba 280, Japan); Hakura, A. *J Cell Physiol* 100(2): 263-272; 1979.

Changes in mitotic capability as a phenotypic expression of cellular transformation was investigated in 121-6-5 cells, a temperature-sensitive (ts) mutant of a polyoma virus-transformed BALB/3T3 cell line. Hyaluronidase treatment of contact-inhibited cells at 39 C induced a single round of cell division, which was then followed by inhibition of cell growth by cell density. However, when the cells were incubated at 35 C following enzyme treatment, the density-inhibition block disappeared and the cells entered a second cycle of cell division. The ability of cells to complete a second division was examined by shifting the cells from 39 C to 35 C during different phases of the first mitotic cycle after the enzyme treatment. Incubation of S phase cells at 35 C for 6 hr did not induce a second round of division. These results suggest that expression of the transformed phenotype in 121-6-5 cells is dependent upon both temperature and stage of mitosis. (26 refs)

79-6436 Kinetics of Reentry of Polyoma Progeny Form I DNA into Replication as a Function of Time Postinfection. (Eng) Roman, A. (Dept. Microbiology and Immunology, Indiana Univ. Sch. Medicine, Indianapolis, IN 46223). *Virology* 96(2): 660-663; 1979.

The fate of polyoma progeny Form I molecules was monitored at different times in the replication cycle. Molecules labeled by a 20-min pulse of [^3H]thymidine at 20 hr postinfection (PI) reentered replication at a greater rate than molecules labeled at 28 hr PI. In addition, a greater proportion of molecules labeled at 20 hr PI reentered replication than molecules labeled at 28 hr PI. However, regardless of the time postinfection examined, progeny molecules appeared to be removed from the replicating pool approx 3 hr following their initial synthesis. When replication was monitored by a continuous label of [^{14}C]BUDR, labeled molecules substituted with BUDR in both strands accumulated continuously for at least 6 hr. (5 refs)

79-6437 Cell-Free Assembly of a Polyoma-like Particle from Empty Capsids and DNA. (Eng) Barr, S. M. (Dept. Cellular and Developmental Biology, Univ. Arizona, Tucson, AZ 85721); Keck, K.; Aposhian, H. V. *Virology* 96(2): 656-659; 1979.

Conditions for the cell-free formation of a stable polyomalike particle (PLP) whose DNA is resistant to the action of pancreatic DNase are reported. A PLP is formed when polyoma DNA and purified empty capsids are incubated in a cell-free system. The DNA of this new particle is protected against the action of pancreatic DNase. The density of the purified PLP in CsCl is 1.32 g/cm^3 , which is intermediate between that of polyoma virions

(1.34 g/cm³) and empty capsids (1.29 g/cm³). Purified PLP sediments at 190S in sucrose and is stable in solns of high ionic strength. The DNA extracted from PLP with the use of a detergent and phenol is double-stranded with a mol wt of approx 1.1×10^6 . The particles are stable in CsCl at 4 C for at least 5 mo. Electron micrographs indicate that highly purified PLP's stained with 2% phosphotungstic acid have the same appearance as polyoma capsids. Neither aggregates nor complexes bound by loose ionic bonds appear reasonable to explain these results. The evidence indicates that the DNA of this new PLP is protected by the capsid. (8 refs)

- 79-6438 Comparisons of Two Early Gene Functions Essential for Transformation in Polyoma Virus and SV-40. (Eng) Fluck, M. M. (Dept. Microbiology and Public Health, Michigan State Univ., E. Lansing, MI 48824); Benjamin, T. L. *Virology* 96(1): 205-228; 1979.

Temperature-sensitive (ts-a) mutants of polyoma virus (PV) were compared with ts-A mutants of simian virus 40 (SV40), and host range transformation defective (hr-t) mutants of PV were compared with the viable deletion mutants of SV40 mapping between 0.54 and 0.59 map units (dl mutants). All four groups of mutants were either totally or partially defective in inducing stable transformation, as assayed by anchorage-independent growth. Two distinct functions essential for transformation were encoded within the early regions of these papovaviruses, and two approaches were taken to define the roles of these early viral genes in cell transformation. In the first approach, a clonal analysis was made of cells transformed at the permissive temperature by ts-a/A mutants. The majority of clones showed no temperature dependence of either selected or unselected properties when compared with wild-type virus-transformed clones. No correlation was seen between the appearance of a temperature-sensitive phenotype in individual clones and the expression of tumor-antigen species at permissive and nonpermissive temperatures. In the second approach, mutants of all four groups were tested for their ability to induce abortive transformation, as measured by the transient loss of anchorage-dependent growth. The ts-a/A mutagens retained their ability to induce abortive transformation, behaving like wild-type virus at the nonpermissive temperature. The hr-t mutants were negative, whereas the dl mutants showed a reduced ability to induce abortive transformation. (115 refs)

- 79-6439 Interrupting the Early Region of Polyoma Virus DNA Enhances Tumorigenicity. (Eng) Israel, M. A. (DNA Recombinant Unit, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20205); Simmons, D. T.; Hourihan, S. L.; Rowe, W. P.; Martin, M. A. *Proc Natl Acad Sci USA* 76(8): 3713-3716; 1979.

The tumorigenicity of DNA from polyoma virus after cleavage with a variety of restriction enzymes was evaluated in suckling Syrian hamsters. Cleavage with enzymes that interrupt the region of the genome coding for the large tumor (T) antigen of polyoma virus markedly enhanced the tumorigenicity above that observed with DNA I of the virus. Cell lines established in vitro from tumors induced by polyoma virions, polyoma virus DNA I, or polyoma virus DNA that had been cleaved with restriction endonucleases in the early region all contained the polyoma virus middle and small T antigens but not the large T antigen. These findings indicate that the large T antigen of polyoma virus is not required for the maintenance of the transformed state and probably not for the initiation of tumorigenesis by viral DNA. (32 refs)

- 79-6440 Structural Changes in Simian Virus 40 Chromatin as Probed by Restriction Endonucleases. (Eng) Liggins, G. L. (Hyland Div., Travenol Lab., Inc., Round Lake, IL 60073); English, M.; Goldstein, D. A. *J Virol* 31(3): 718-732; 1979.

The structure of simian virus 40 (SV40) chromatin was studied through its use as a substrate for single- and multiple-site bacterial restriction endonucleases. Approximately the same fraction of the chromatin DNA was cleaved by each of three different single-site endonucleases, indicating that the nucleosomes do not have unique positions with regard to specific nucleotide sequences within the population of chromatin molecules. However, the extent of digestion was strongly influenced by salt concentration. At 100 millimolar (mM) NaCl-5mM MgCl₂, only about 20% of the SV40 DNA I in chromatin was converted to linear SV40 DNA II. In contrast, at lower concentrations of NaCl (0.05 or 0.01 M), an additional 20 to 30% of the DNA was cleaved. These results suggest that at 100 mM NaCl only the DNA between nucleosomes was accessible to the restriction enzymes, whereas at the lower salt concentrations, DNA within the nucleosome regions became available for cleavage. When SV40 chromatin was digested with multiple-site restriction enzymes, less than 2% of the DNA was digested to limit digest fragments, whereas only a small fraction (9% to 15%) received two or more cuts. Instead, the principal digest fragment was full-length linear SV40 DNA II. The failure to generate limit digest fragments was not a consequence of reduced enzyme activity in the reaction mixtures or of histone exchange. When the position of the principal cleavage site was mapped after *HpaI* digestion, it was found that this site was not unique. Nevertheless, all sites were not cleaved with equal probability. An additional finding was that SV40 chromatin containing nicked-circular DNA II produced by random nicking of DNA I was also resistant to digestion by restriction enzymes. These results suggest that the initial cut which causes relaxation of topological constraint in SV40 chromatin DNA imparts resistance to further digestion by restriction enzymes. This effect may be accomplished by either "winding" of the internucleosomal DNA into the body of the nucleosome or by successive right-hand rotation of nucleosomes. (66 refs)

- 79-6441 A Poly(dT)-stimulated ATPase Activity Associated with Simian Virus 40 Large T Antigen. (Eng) Giachero, D. (Dept. Biochemistry, Univ. Illinois, Urbana, IL 61801); Hager, L. P. *J Biol Chem* 254(17): 8113-8116; 1979.

Highly purified SV40 large T antigen ATPase activity was stimulated approx 7-fold by the DNA homopolymer poly(dT). The poly(dT)-stimulated enzyme hydrolyzed various ribonucleotide and deoxyribonucleotide triphosphates, with ATP and deoxyATP serving as the best substrates. Purified large T antigen hydrolyzed ATP to adenosine diphosphate and inorganic phosphate (P_i), with a max specific activity of 13.5 μ moles of P_i released per hr per mg of protein. Of the various natural and synthetic polynucleotides tested, poly(dT) was by far the best activator. Long chain poly(dT) molecules proved to be much more effective activators than short chain length oligo(dT) molecules. The highly purified large T antigen contained no detectable protein kinase activity. (30 refs)

- 79-6442 Papovaviruses as Vehicles for the Transduction of Foreign Genes into Mammalian Cells. (Eng) Upcroft, P. (Dept. Microbiology and Immunology, Univ. California, Los Angeles, CA 90024); Ziemer, F.; Skolnik, H.; Fareed, G. C. *Brookhaven Symp Biol* (29): 207-217; 1978.

The hybrid simian virus 40 (SV40)-*Escherichia coli* DNA (SV40-*su*+III), which conserves the origin of replication and the A gene function of SV40, was found to transform secondary rat embryo cells, using the calcium transfection technique. Reassociation kinetics confirmed that the rat cells were transformed by DNA that had the structure of the hybrid SV40-*su*+III. Both SV40 and *E. coli su*+III DNA sequences were localized by hybridization on specific DNA fragments. An unexpected observation was the presence of free (unintegrated) as well as integrated hybrid viral DNA sequences. In another experiment, the TC7 subline of CV-1 African green monkey kidney cells was infected with the SV40-*su*+III DNA by the DEAE-dextran procedure and 48 hr later the cells were subcultured and serially diluted for cell cloning. Of a large number of cloned lines from the original DNA-infected cell culture, two cell populations that carried substantial amounts of free DNA were identified. Subcloning of cells from these persistently infected cell cultures revealed the persistence of free viral DNA in most subclones and expression of SV40 intranuclear T antigen. These studies show that both the SV40 vector and bacterial DNA sequences remain associated with transformed rat embryo cells and persistently infected monkey kidney cells. (19 refs)

- 79-6443 Simian Virus 40 Gene Expression in Permissive, Nonpermissive, and Virus-resistant Cells. (Eng) Graessmann, A. (Inst. Molecular Biology and Biochemistry, Free Univ. Berlin, West Berlin 33, W. Germany); Graessmann, M.; Mueller, C. *Brookhaven Symp Biol* (29): 197-206; 1978.

Simian virus 40 (SV40) gene expression was compared in infected nonpermissive 3T3 mouse cells and in 3T3 cells microinjected with viral DNA. In virus-infected cells, both the onset of accumulation of intranuclear T-antigen and the proportion of T-antigen-positive cells correlated with the multiplicity of infection (MOI). When confluent infected mouse cells were stimulated for DNA synthesis, there was neither demonstrable viral DNA replication nor viral capsid antigen (V-antigen) synthesis, even at a MOI of 1,000 plaque-forming units. However, T-antigen synthesis was demonstrable in 3T3 cells at 12 hr and V-antigen synthesis at 24 hr after microinjection of 1 mg DNA I/ml injection buffer. SV40 V-antigen synthesis was directly correlated with the number of injected DNA I molecules. Late SV40 gene expression appears to require the efficient synthesis of the virus-coded T-antigen. In both nonpermissive mouse cells and permissive monkey cells, V-antigen synthesis was demonstrable only if a threshold amount of intranuclear T-antigen was obtained. When isolated SV40 replicative intermediate DNA (RI-DNA) was microinjected into monkey kidney cells preincubated with an inhibitor of DNA synthesis, 30% of the recipient cells synthesized SV40 V-antigen within 24 hr. Following a 10-fold higher amount of DNA I, only T-antigen was detectable. These results indicate that late viral gene transcription depends on the availability of a template structure generated during the process of viral DNA replication. (23 refs)

- 79-6444 Sites Including Those of Origin and Termination of Replication Are Not Freely Available to Single-Cut Restriction Endonucleases in the Supercompact Form of Simian Virus 40 Minichromosome. (Eng) Das, G. C. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Allison, D. P.; Niyogi, S. K. *Biochem Biophys Res Commun* 89(1): 17-25; 1979.

Conditions for the isolation of compact forms of the simian virus 40 (SV40) minichromosome from both virions and infected African green monkey kidney cells (BSC-1) were studied.

Minichromosomes isolated from both virions (MV) and infected cells (MI) had highly compact structures in buffer containing 0.15 M NaCl, and they sedimented with S values of about 90-100 and 115-130, respectively. MI also appeared to be the more compact of these structures under the electron microscope. Only 30%-35% of the sites of origin and termination of replication in MV were freely available to the restriction endonucleases *Bgl*I and *Bam*HI. MV were similarly resistant to *Eco*RI and *Hpa*II. In contrast, almost no sites in MI were available to any of these single-cut endonucleases. In 0.6 M NaCl, MV and MI changed to relaxed structures of 45S-55S and 50S-60S, respectively, containing 20-24 nucleosomes per genome. They also became more sensitive to *Bgl*I, *Bam*HI, *Eco*RI, and *Hpa*II. (28 refs)

- 79-6445 Antigenic Relationship of SV40 Early Proteins to Purified Large T Polypeptide. (Eng) Lanford, R. E. (Dept. Virology, Baylor Coll. Medicine, Houston, TX 77030); Butel, J. S. *Virology* 97(2): 295-306; 1979.

Rabbit antiserum was produced against SV40 large T antigen purified by immunoprecipitation and sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. This antiserum immunoprecipitated both large T and small t antigens and reacted with SV40, T, U, and S antigens by immunofluorescence. These data establish the antigenic relatedness of all the known SV40 early gene products, with the exception of transplacental antigen activity, and confirm the virus-specific nature of each. The reactivity of the anti-T polypeptide serum was compared with the specificities of T-reactive antisera produced by different methods, including conventional tumor-bearing hamster sera, rabbit antiserum directed against whole-cell SDS-lysates of SV40-transformed rabbit kidney cells, and high-liter ascites fluid from hamsters (ascites induced by injection of SV40-transformed hamster ascites cells). Each of the antisera was reactive in all of the tests for SV40-induced early antigens, but the relative reactivity toward each protein varied considerably. It is postulated that the differences in reactivity to small t antigen and U antigen represent differences in the immune response of individual animals to the amino and carboxyl termini of the large T antigen polypeptide, respectively. Antiserum produced against the SDS-denatured large T polypeptide exhibited the highest reactivity to both small t and U antigenic sites relative to its reactivity against intranuclear large T antigen. (50 refs)

- 79-6446 The Influence of Fluorophenylalanine on the Synthesis of Simian Virus 40 DNA and T Antigens. (Eng) Kress, M. (Unites d'Immunologie et de Physiologie des Virus, Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800 Villejuif, France); Girard, M. *Biochimie* 61(3): 419-423; 1979.

The influence of fluorophenylalanine (FPA) on the synthesis of simian virus 40 (SV40) DNA and tumor (T) antigens was investigated in CV1 monkey cells infected with the VA 4554 strain of SV40. Treatment of these cells with FPA resulted in an increased uptake of thymidine by the cells and progressive inhibition of both viral and cellular DNA synthesis. Viral DNA synthesis was more sensitive to the inhibition than cellular DNA synthesis. SV40 T-antigen synthesis was unaffected by FPA, as judged from the results of immunofluorescence assays. The mol wt of the major polypeptides immunoprecipitated from cell extracts by antibodies from tumor-bearing hamster sera was also unaffected. It is suggested that T antigen synthesized in the presence of FPA is non-functional. (22 refs)

- 79-6447 Roles of the Simian Virus 40 Tumor Antigens in Transformation of Chinese Hamster Lung Cells: Studies with Simian Virus 40 Double Mutants. (Eng) Martin, R. G. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20205); Setlow, V. P.; Edwards, C. A. *J Virol* 31(3): 596-607; 1979.

Simian virus 40 (SV40) mutants containing both a *tsA* mutation [rendering the 90,000 mol wt (90K) T-antigen thermolabile] and a deletion between 0.54 and 0.59 map units (reducing the size and amount of the 20K t-antigen) were used to study the roles of SV40 tumor antigens in the transformation of Chinese hamster lung (CHL) cells. SV40 mutants with deletions between 0.54 and 0.59 map units failed to transform resting cells; but actively growing CHL cells were transformed at comparable rates by wild-type, *tsA*, and *tsA*-deletion mutant virus. The frequency of transformation by the double mutants was markedly reduced relative to the *tsA* mutants when resting rather than growing cells were used in the transformation assays. The double mutants, like the *tsA* mutants, were unable to transform growing or resting CHL cells at the nonpermissive temperature. Growth-arrested cells were transformed by the deletion mutants at less than 2% the frequency found when the 20K t-antigen was normal. Growth arrest had very little effect on the temperature sensitivity of the resulting transformed cell line whether or not the deletion was present. (24 refs)

- 79-6448 Assessment of Host Immune Status During Progressive Growth and After Excision of DNA Virus (Simian Virus 40) Tumors in Hamsters: Comparison of Tumor-specific and Tumor-unrelated Parameters of Immune Responsiveness. (Eng) Houston, K. J. (Dept. Medicine, Univ. Medical Center, Jackson, MS 39216); Blasecki, J. W. *J Natl Cancer Inst* 63(3): 665-673; 1979.

The kinetics of cellular immune responses to simian virus 40 (SV40) tumor-specific transplantation antigen (TSTA) were compared with the kinetics of responses to T- and B-cell mitogens and tumor-unrelated antigens in inbred MHA/SsLAK hamsters during the course of progressive syngeneic SV40 tumor growth and following tumor excision. Using the tumor cell neutralization test in vivo and the macrophage migration inhibition assay in vitro, specific cellular immunity to TSTA was detected within 4 days after tumor cell inoculation, when the tumor was small; this response was no longer detected after 7 days, when the tumor had reached a diameter of 12.5 mm, but it returned 14 days after tumor excision. The kinetics of the mitogen responses of spleen cells from tumor bearing hamsters generally showed a lack of correlation with the kinetics of tumor-specific cellular immunity. Suppression of the response to pokeweed mitogen was observed 14 days after tumor inoculation, and suppression of phytohemagglutinin responsiveness was detected 21 days after inoculation. Concanavalin A responses were either at or above control levels at all times. The kinetics of the humoral immune response to murine RBC correlated much more closely with the kinetics of tumor-specific immunity than did the responses to mitogens. IgG antibody (T-dependent) responses were more affected by progressive tumor growth than were IgM (T-independent) responses. The data suggest that, when tumor-unrelated assay procedures are used to assess the immune status of cancer patients, an accurate picture may not be obtained even with a battery of such tests. (43 refs)

- 79-6449 Reactivation of Silent rRNA Genes by Simian Virus 40 in Human-Mouse Hybrid Cells. (Eng) Soprano, K.

J. (Dept. Pathology and Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Dev, V. G.; Croce, C. M.; Baserga, R. *Proc Natl Acad Sci USA* 76(8): 3885-3889; 1979.

Mouse-human hybrid cells were used to study the ability of simian virus 40 to regulate the expression of ribosomal RNA (rRNA) genes in vivo. In these hybrid cells, only the rRNA genes of the dominant species are expressed. The genes for the rRNA of the recessive species are silent. Simian virus 40 infection of the hybrids led to the production of two distinct 28S rRNA species as analyzed by agarose/2.4% polyacrylamide gel electrophoresis. These species were identified as human and mouse rRNAs. This result was confirmed by histochemical studies that indicated that the nucleolus organizer regions of both mouse and human chromosomes were actively synthesizing rRNA in the virus-infected hybrid cells. These results indicate that simian virus 40 infection can induce the expression of otherwise silent rRNA genes. (29 refs)

- 79-6450 Evidence for Non-spliced SV40 RNA in Undifferentiated Murine Teratocarcinoma Stem Cells. (Eng) Segal, S. (Lab. Experimental Pathology, NIAMDD, NIH, Bethesda, MD 20014); Levine, A. J.; Khoury, G. *Nature* 280(5720): 335-338; 1979.

The F-9 line of mouse teratocarcinoma cells infected with simian virus 40 (SV40) was used to study the basis for the absence of expression of SV40 genetic information in such cells. Using polyacrylamide gel electrophoresis, two distinct polypeptides with apparent mol wts of 105,000 and 55,000 were identified after immunoprecipitation with anti-SV40 tumor (T) serum. SV40 T antigens were not detected in the infected F-9 cells. The in vitro sarkosyl method for the detection of viral transcription demonstrated that viral transcription was initiated in SV40-infected F-9 cells, substantial fractions of viral transcription being initiated on both early and late viral DNA strands. Determinations of the proportion of the SV40 genome that is transcribed in vivo demonstrated the presence of two spliced early SV40 messenger RNA's (mRNA's) coding for T and t antigens. Spliced early mRNA was shown to be synthesized during the infection of differentiated mouse embryo cells by SV40, the mature cytoplasmic spliced RNA's being derived from this primary transcript. The data indicate that a major block to SV40 gene expression in F-9 cells is related to their inability to splice the primary transcripts. (27 refs)

- 79-6451 The 55K Protein on the 5' Termini of Adenovirus Type 2 DNA Is Unrelated to Virus-coded Candidate Transformation Proteins (E1-53K, E1-40K-50K) and DNA-Binding Proteins (E2-42K/47K/73K). (Eng) Green, M. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63110); Wold, W. S.; Brackman, K. H.; Cartas, M. A. *J Virol* 31(3): 836-840; 1979.

Further investigations are reported on a polypeptide of 55,000 daltons (55K) that has been shown to be linked, probably covalently, to the 5'-termini of adenovirus type 2 DNA, is synthesized during early stages of infection, and thus may function in viral DNA replication, gene regulation, or cell transformation. Several virus-coded early polypeptides have been identified that could correspond to the terminal 55K, including the E1-40K-50K and E1-53K candidate transformation polypeptides and the E2-42K/47K/73K single-stranded DNA-binding polypeptide. Two-dimensional trypt-

tic [35 S]methionine-peptide maps of the terminal 55K, however, differed completely from [35 S]methionine-peptide maps of four related E1-40K-50K polypeptides, the E1-53K, and the related E2-42K, E2-47K, and E2-73K polypeptides. It was concluded that the terminal 55K polypeptide does not correspond to any of the known virus-coded early polypeptides. (18 refs)

- 79-6452 Adenovirus Type 2 Terminal Protein: Purification and Comparison of Tryptic Peptides with Known Adenovirus-coded Proteins. (Eng) Harter, M. L. (Cold Spring Harbor Lab., Cold Spring Harbor, New York, NY 11724); Lewis, J. B.; Anderson, C. W. *J Virol* 31(3): 823-835; 1979.

The protein covalently bound to the 5' termini of adenovirus type 2 DNA was purified from virus labeled with [35 S]methionine. Using exclusion chromatography of disrupted virions, the DNA-protein complex was isolated and was then digested with DNase. The terminal protein isolated from mature virus was most effectively labeled if the cells were exposed to [35 S]methionine during the "intermediate" period of 13 to 21 hr postinfection, suggesting that the protein is synthesized during this interval. The tryptic peptides of the terminal protein were compared with those of several known adenovirus-coded proteins and found to be unrelated. In particular, the terminal protein was not related to the 38-50K early proteins encoded by the leftmost 4.4% of the adenovirus genome, one region essential for the transforming activity of the virus; nor was it related to the 72K single-strand-specific DNA binding protein, the minor virion component IVa₂, or the major capsid component hexon. (45 refs)

- 79-6453 A Spliced Sequence at the 5'-Terminus of Adenovirus Late mRNA. (Eng) Berget, S. M. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Sharp, P. A. *Brookhaven Symp Biol* (29): 332-344; 1978.

Poly(A)-containing RNA was isolated from polyribosomes prepared 32 hr after infection with adenovirus type 2 (Ad2) and fractionated on polyacrylamide gels. The predominant viral messenger RNA (mRNA) isolated by this procedure was that coding for the major virion capsid polypeptide, hexon (II). This RNA was mapped by hybridizing the purified hexon (II) mRNA to restriction endonuclease fragments of Ad2 DNA under R-loop conditions and ultrastructural study of the hybrids. The hexon (II) mRNA mapped within 51.7 and 61.3 units on the viral genome. Electron microscopy of hybrids formed between purified hexon (II) mRNA and single-stranded *Hind*III A DNA showed that the 5'-end of hexon (II) mRNA consists of 160 bases of RNA covalently attached to the main body of the RNA and not coded for by DNA sequences adjacent to those coding for the rest of the mRNA. Experiments involving hybridization of purified hexon (II) mRNA to single-stranded Ad2 *Eco*RI A DNA indicated that these spliced sequences are complementary to three regions of the viral genome located at 17, 20, and 27 units. These three sequences are arranged tandemly in the tail sequences in the order in which they are found on the genome, which suggests that the leader sequences might have become attached to the remainder of the mRNA following looping back, excision, and ligation of an initial large nuclear transcript. This model requires the existence of an RNA ligase in mammalian cells and some control element, either a protein or a small RNA. (29 refs)

of Human Adenovirus Type 2. (Eng) Green, M. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, 3681 Park Ave., St. Louis, MO 63110); Wold, W. S.; Brackmann, K. H.; Cartas, M. A. *Virology* 97(2): 275-286; 1979.

Antisera against four lines of adenovirus (Ad) 2-transformed rat cells, including F17 cells which contain only early gene region 1 (map position 1.5-11, the transforming region), can immunoprecipitate major polypeptides of 53,000 (53K) and 15,000 (15K) daltons. The 53Ks precipitated by three of these antisera as well as Ad1-SV40 induced hamster tumor sera were all shown to possess identical two-dimensional tryptic [35 S]Met-peptide maps. Similarly, all 15Ks precipitated by these antisera had identical maps. Tryptic and chymotryptic maps demonstrated that most if not all of the [35 S]Met-peptides of 15K are shared by 53K. Four [35 S]Met-labeled polypeptides of 40K-50K, specific to Ad2 early infected human cells, were isolated in O'Farrell-type 2D gels. These polypeptides are coded within map position 1.5-4.5, whereas the 53K and 15K are coded within map position 4.5-11. As expected, tryptic and chymotryptic peptide maps of these four polypeptides indicated no relationship to 53K or 15K. Two of the 40K-50K polypeptides were highly related, the other two were highly related, and all four were partially related. In addition to 53K and 15K, the F17 antiserum precipitated a 28K polypeptide and minor bands of 14K-16K, 18K-20K, and 11K-12K. Tryptic and chymotryptic maps of these polypeptides showed that 14K-16K and 18K-20K polypeptides are members of the 53K/15K family, 11K-12K polypeptides are related to each other but are unrelated to any other polypeptides, and 28K is unrelated to any other polypeptides. It was concluded that early region 1 codes for two (53K/15K family, 40K-50K family) or possibly more (eg, 11K-12K family) families of polypeptides; the polypeptides included in each family overlap in amino acid sequence and therefore may be translated from overlapping spliced messenger RNAs. The possible contribution of these polypeptides to the phenotype of Ad2-transformed cells is discussed. (48 refs)

- 79-6455 Protease of Adenovirus Type 2: Partial Characterization. (Eng) Bhatti, A. R. (Departement de Microbiologie, Centre Hospitalier Universitaire, Université de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada); Weber, J. *Virology* 96(2): 478-485; 1979.

An adenovirus type 2 (Ad2)-associated protease activity specific for the cleavage of core polypeptide PVII to polypeptide VII was identified, and its properties were studied in an in vitro assay system. All temperature-sensitive (ts) mutants examined failed to induce protease activity at 39 C. Activity was restored in the revertants. The protease activity was inhibited completely by 1 mM tosylamide phenylethylchloromethyl ketone, but phenylmethylsulfonylfluoride and tosyllysinechloromethyl ketone at 1 mM reduced enzyme activity to 36% and 10% of control values, respectively. In contrast, EDTA had no effect. Optimum enzyme activity was observed at neutral pH. Enzyme activity was stable up to, but not beyond, 45 C. Polypeptide PVII was cleaved whether it was in the soluble, bound, or heat- or acid-precipitated form. Wild-type young virions contained endogenous protease activity, but the virions produced at 39 C by ts1-infected cells did not. The PVII contained in these ts1-39 virions, however, may be processed by exogenous wild type enzyme after the particles have been frozen-thawed several times. These results suggest that Ad2-associated protease is a chymotrypsinlike, nonmetallo-, neutral protease. (26 refs)

- 79-6454 Identification of Families of Overlapping Polypeptides Coded by Early "Transforming" Gene Region I

- 79-6456 In Vitro Translation Products Specified by the Transforming Region of Adenovirus Type 2. (Eng)

Halbert, D. N. (Dept. Pathology, Div. Biology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO 63110); Spector, D. J.; Raskas, H. J. *J Virol* 31(3): 621-629; 1979.

Proteins specified by purified region 1 RNAs of adenovirus type 2 were characterized. Region 1 RNAs were purified by hybridization selection, using restriction fragments bound to nitrocellulose membranes, and by size fractionation. The isolated RNAs were then translated in cell-free systems derived from wheat germ and rabbit reticulocytes. The family of RNAs specified by 0 to 4.4 sequences includes two RNAs, which are 12S and 13S in size; these were partially separated by mol wt and translated. The 13S RNA produced 53,000-dalton (53K) and 41K peptides, and the 12S RNA synthesized 47K and 35K products. The family of RNAs mapping from 4.4 to 11.0 encoded three separate polypeptides, each of which could be assigned to a specific RNA. A 12K product that comigrated with structural polypeptide IX was synthesized from the 9S RNA, as previously reported. The 13S RNA encoded a 15K polypeptide that corresponded to a 15K polypeptide in infected cell extracts. The 22S RNA encoded a 52K protein distinct from the 0 to 4.4 polypeptides. (46 refs)

79-6457 On the Mechanism of Arginine Requirement for Adenovirus Synthesis. (Eng) Plaat, D. (Departement de Microbiologie, Centre Hospitalier Universitaire de l'Université de Sherbrooke, P.Q., J1H 5N4, Canada); Weber, J. *Arch Virol* 60(3/4): 187-196; 1979.

The effects of arginine (AG) deprivation at different times during infection with human adenovirus type 2 on the synthesis and processing of viral proteins, on the assembly of incomplete and complete virions, and on the activity of polypeptide PVII-specific endoprotease were studied. AG deprivation greatly reduced the synthesis of all viral proteins, particularly the precursor to core protein VII. The inhibition was completely reversible by the addition of AG to the medium. AG deprivation between 7 and 20 hr postinfection inhibited the processing of PVII to VII, suggesting that PVII is not cleaved autocatalytically. The assembly of incomplete virions was sensitive to AG deprivation between 0 and 20 hr postinfection, but the assembly of complete virions was dependent on the continuous presence of AG. This observation supports the hypothesis that incomplete virions are precursors of complete virions. Experiments on PVII-specific endoprotease activity showed that AG deprivation caused only a slight reduction in *in vitro* activity, although no activity was observed *in vivo*. The results lead to the hypothesis that AG deficiency inhibits the synthesis of a functional protein essential for virion maturation, other than the synthesis or processing of PVII. (18 refs)

79-6458 Association of Tumor Induction by Ultraviolet Light-inactivated Adenovirus 2-Simian Virus 40 Recombinants with a Specific Segment of Simian Virus 40 DNA. (Eng) Lewis, A. M. (Office Scientific Director, Natl. Inst. Allergy and Infectious Diseases, NIH, Public Health Service, Dept. Health, Education and Welfare, Bethesda, MD 20205); Cook, J. L. *J Natl Cancer Inst* 63(3): 695-705; 1979.

The development of virus-induced tumors was studied in Syrian golden hamsters neonatally inoculated sc with 0.1 ml of adenovirus type 2 (Ad2), nondefective (ND) Ad2-Simian virus 40 (SV40) hybrids (Ad2*ND₂ and Ad2*ND₄), or B55 virus that had been inactivated by UV. Four of 27 and 3/34 hamsters inoculated with UV-inactivated Ad2*ND₄ virus, which contains the segment of the SV40 genome between map positions 0.11 and 0.59,

developed tumors; 1/33 hamsters inoculated with the inactivated B55 hybrid developed tumors. One of 31 animals inoculated with 8-16 U of Ad2-neutralizing antibody also developed a tumor. The tumors were either SV40-type fibrosarcomas (4/9), Ad2-type small cell sarcomas (2/9), or a mixture of these types (3/9). Ad2 and the Ad2*ND₂ hybrid, which contains the segment of the SV40 genome between map positions 0.11 and 0.43, were not oncogenic after inactivation by UV. Tumors removed from hamsters inoculated with the inactivated Ad2*ND₄ and B55 viruses contained serologically detectable virus-specific Ad2 T- and SV40 T-antigens. Ad2- and SV40-specific antibodies were detected in sera from hamsters carrying primary and transplanted neoplasms by complement fixation and fluorescent antibody assays. These results indicate that the incorporation of a specific segment of SV40 DNA into the Ad2 genome can alter the pathogenesis of the Ad2*ND₄ virus by rendering it oncogenic for hamsters. (58 refs)

79-6459 Type C Particles in Culture of Human Glioblastoma Cells. (Eng) Yutani, C. (Dept. Pathology, Natl. Cardiovascular Center, 125 Fujishirodai Suita, Osaka 565, Japan); Satoh, M.; Kanai, N.; Kitamura, H.; Hori, M.; Hayakawa, T.; Nakagawa, H.; Sakamoto, Y.; Nakata, Y. *Acta Pathol Jpn* 29(4): 643-652; 1979.

Biochemical, virological, and electron microscope studies were made of a human glioblastoma cell culture after 10-15 passages. The cultures produced reverse transcriptase activity. ³H-uridine was incorporated into particles with a buoyant density of 1.07 g/ml, equal to that of oncornavirus (OV) particles. ³H-thymidine was not incorporated, which suggests that the virus particles contain only RNA as their nucleic acid. Reverse transcriptase activity was also demonstrated in the particles, suggesting that the cultured human glioblastoma cells were producing C-type OV. Ultrastructural observations of the cell culture showed many viruslike particles whose morphological features were characterized by three electron-dense, ring-shaped, membranelike shells (envelope) surrounding a relatively electron-lucent core, consistent with mature OV. The mean diameter of the particles was approx 100 nanometers (nm). Spikes measuring 1.1 nm protruded from the outer layer. Budding of the virus was seen on the surface of the tumor cells. (18 refs)

79-6460 Assay of Mouse-Cell Clones for Retrovirus p30 Protein by Use of an Automated Solid-State Radioimmunoassay. (Eng) Kennel, S. J. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Tennant, R. W. *Virology* 97(2): 464-467; 1979.

A solid-state radioimmunoassay (SS-RIA) was developed for retrovirus protein p30 that is suitable for large-scale application. Secondary antibody bound to Sepharose beads is used to bind antigen-antibody complexes, which can subsequently be separated from free antigen by an automated cell harvester in a microtiter plate system. Using this assay, 50% competition was achieved with 1 nanog of unlabeled p30 showing its usefulness for quantitation in the 0.5-5.0 nanog range. Assays for interspecies and type-specific antigenic determinants of p30 were used to identify clones of cells producing this protein. Cell clones identified in the interspecies SS-RIA were assayed for virus production by fluorescent antibody tests. Of 15 clones tested, 11 were positive in the FA test. Clones positive in the SS-RIA for type-specific p30 determinants were analyzed by quantitative fluid-phase RIA; both assays gave identical results. It is claimed that one investigator can analyze up to

1,000 clones/day for p30 production and that the assays are sensitive and give reproducible results. (9 refs)

- 79-6461 Molecular Evidence for a Type C Retrovirus Etiology of the Lymphoproliferative Disease of Turkeys. (Eng) Gazit, A. (Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ., Tel-Aviv, Israel); Yaniv, A.; Ianconescu, M.; Perk, K.; Aizenberg, B.; Zimber, A. *J Virol* 31(3): 639-644; 1979.

The role of a new type C retrovirus isolated from the blood of turkeys infected with lymphoproliferative disease (LPD) in the etiology of LPD was studied. The virus is distinct from the avian leukosis-sarcoma virus complex and the reticuloendotheliosis virus (REV) group. LPD complementary DNA (cDNA) hybridized readily to cellular RNA from LPD tumors but not to that from REV-induced tumors or normal turkey embryos. Approx 0.16% of LPD tumor RNA appeared to be virus specific. REV cDNA did not hybridize with cellular RNA from LPD virus-induced tumors or with RNA from normal turkey tissues. Melting temperatures for RNA-cDNA hybrids of LPD virus and REV were 88 and 85 C, respectively. LPD viral cDNA readily associated with cellular DNA from LPD tumors, the melting point of the hybrids being 82 C. LPD cDNA annealed to a much lower extent with a lower degree of base pair homology (melting point 77 C) with DNA from REV-induced tumors. Normal turkey and chicken DNA and the DNA of other species examined lacked LPD viral sequences, suggesting that LPD virus is not an endogenous virus of turkeys. (32 refs)

- 79-6462 Polypeptide Profile of HBsAg Excreted by a Human Hepatoma Cell Line. (Eng) Monjardino, J. (Div. Cell Studies, Clinical Sciences Building, Royal Free Hosp., Pond St., London NW3 2QG, England); Crawford, E. *Virology* 96(2): 652-655; 1979.

The polypeptide composition of hepatitis B surface antigen (HBsAg) particles secreted by a human hepatoma cell line (Alexander) was analyzed. Five major components with mol wts of 22,000, 28,000, 33,000, 38,000, and 49,000 were identified. The two smaller species (mol wts of 22,000 and 28,000) were found to be the major components. The polypeptide profile was similar to that described for HBsAg derived from the sera of acute hepatitis patients and chronic carriers. Data suggesting that the various HBsAg polypeptide components are aggregates and glycosylated derivatives of the 22,000-dalton polypeptide subunit are presented. (13 refs)

- 79-6463 Possible Role of Viruses or Virus-like Factor(s) in Malignancies of Animal and Microbial Cells. (Eng) Babbar, O. P. (Central Drug Res. Inst., Chattar Manzil Palace, Lucknow-226001, India). *Indian J Med Res* 69: 874-885; 1979.

The possible role of viruses or viruslike factor(s) in animal and microbial cell malignancies was studied. Mortality and lesions or symptoms characteristic of mycoplasma infections were observed in chick embryos and 1-day-old chicks infected with avian mycoplasma strains DPV or F5V but not in those infected with strains F5 or DP. Mortality and disease in plant embryos infected with DPV or F5V were greater than in those infected with DP or F5. Lysates prepared from $2-4 \times 10^7$ DPV cells or $1-6 \times 10^6$ F5V cells caused mortality and typical lesions in chick and plant em-

bryos, whereas 100-fold higher concentrations of lysates from DP or F5 cells were nonlethal in chick embryos and much less harmful in plant embryos. These results suggested that the virulence of DPV and F5V was due to their increased synthesis of toxic factor(s). The biochemical properties of DPV and DP and those of F5V and F5 did not differ, but the duration of exponential phase growth required by DPV and F5V to reach a max concentration of cells was longer than that of DP and F5. DPV and F5V grown in the presence of chick interferon (CIF) lost their virulence for chick embryos and behaved like DP and F5. With increasing CIF concentrations in the growth media, the number of *Salmonella typhimurium* (nonlysogenic) or *Escherichia coli* (lysogenic) required per mouse to cause 50% mortality increased. CIF-induced inhibition of endotoxin production by these organisms led to a corresponding increase in their rate of multiplication. CIF-induced inhibition of the production of exotoxins by *Staphylococcus aureus* and *Clostridium welchii* also led to an increase in their rate of multiplication. CIF appeared to block only those functions of Walker 256 carcinoma cells associated with their malignancy, and it had no direct cytotoxic effect on them. These results indicate that (1) the production of toxins in nonlysogenic pathogenic bacterial cells may be initiated by a cellular gene activated to assume such a function and that (2) malignancy in animal cells may be initiated by genes activated to function as oncogenes. (26 refs)

- 79-6464 Further Characterization of Mengo Subviral Particles: A New Hypothesis for Picornavirus Assembly. (Eng) Lee, P. W. (Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC 27710); Colter, J. S. *Virology* 97(2): 266-274; 1979.

The "50S particle" found in Mengo virus-infected L cells was further characterized. Centrifugal analysis in sucrose density gradients gave an estimated sedimentation coefficient of 53S. When, during the isolation of 53S particles, the KCl concentration in the suspending buffer was increased to 150 mM or higher, some of the particles were converted to structures having a significantly larger sedimentation coefficient. A similar conversion of 53S to more rapidly sedimenting particles occurred when the former were centrifuged to equilibrium in a CsCl density gradient. The sedimentation coefficient of this new particle was estimated to be 75S. Mol wt determinations of the previously described 14 S particles and of the 53S and 75S particles by means of Sepharose 4B exclusion chromatography suggested that the molecular compositions of these particles are $(\epsilon\alpha\gamma)_3$, $(\epsilon\alpha\gamma)_{25}$, and $(\epsilon\alpha\gamma)_{50}$, respectively. Based on these data and on previously reported evidence suggesting a precursor role for the 53S particles, a new hypothesis for the mechanism of Mengo virus assembly is proposed according to which the viral RNA interacts with either a 75S particle or two 53S particles to form a complex represented by $\text{RNA}[(\epsilon\alpha\gamma)_5]_{10}$ before assembly is completed by the addition of two 14S subunits. (19 refs)

See also:

- *(Rev.): 79-6072, 79-6073, 79-6074, 79-6075, 79-6076, 79-6077, 79-6078, 79-6079, 79-6080, 79-6081, 79-6083, 79-6127.
*(Chem.): 79-6227.
*(Phys.): 79-6355, 79-6356, 79-6366, 79-6377.
*(Immun.): 79-6479, 79-6483, 79-6486, 79-6498, 79-6501, 79-6506, 79-6509.
*(Path.): 79-6524, 79-6532, 79-6538, 79-6543.

- 79-6465 Interaction Between Mitogenic Lectins and Lymphocyte Plasma Membranes. (Rus) Sitkovskii, M. V. (Lab. Physicochemistry Biological Membranes, M. V. Lomonosov State Univ., Moscow, USSR); Shestakova, S. V.; Kozlov, Iu. P. *Biull Eksp Biol Med* 88(7): 89-91; 1979.

An attempt was made to evaluate the possible molecular mechanism of lymphocyte activation. A purified suspension of mesenteric lymph node cells from Wistar rats was incubated with medium containing concanavalin A (Con A) or phytohemagglutinin (PHA). After 14- or 20-hr of incubation, the cells were washed, and Con A or PHA was added again. Replacement of Con A by PHA induced DNA synthesis, but each mitogen alone did not induce DNA synthesis. (7 refs)

- 79-6466 Mutagen-induced Disturbances in the DNA of Human Lymphocytes Detected by Antinucleoside Antibodies. (Eng) Bases, R. (Dept. Radiology, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY 10461); Rubinstein, A.; Kadish, A.; Mendez, F.; Wittner, D.; Elequin, F.; Liebeskind, D. *Cancer Res* 39(9): 3524-3530; 1979.

The antinucleoside antibody (ANA) method for studying the action of alkylating mutagens on the DNA of human cells was applied to human peripheral blood lymphocytes (PBL). N-Methyl-N'-nitro-N-nitrosoguanidine, methyl methanesulfonate, and N-nitrosomethylurea induced immunoreactivity to ANA's in human PBL in vitro. This could also be detected in lymphocytes taken from a patient soon after iv administration of cyclophosphamide. The immunoreactivity response, which indicates denatured DNA or DNA single-strand breaks, was scored by immunofluorescent or immunoperoxidase techniques. Examination of blood from 10 normal subjects showed that $32 \pm 4\%$ (SE) of resting PBL were immunoreactive to ANA's. These naturally occurring immunoreactive lymphocytes were largely accounted for by a subpopulation of thymus-derived lymphocytes bearing the Fc receptor for IgM. The presence of these cells did not interfere with the use of PBL for in vitro measurement of additional immunoreactivity caused by alkylating mutagens. The response proved to be dose dependent; up to 90% of lymphocytes could be rendered immunoreactive. Parallel studies with HeLa cells showed a similar dose-response relationship between mutagen action and immunoreactivity. With some agents, the immunoreactivity technique detected effects at lower concentrations than those at which effects could be detected by HeLa cell survival studies. With N-nitrosomethylurea, measurement of DNA repair synthesis by [³H]thymidine autoradiography showed that in HeLa cells, these two parameters of response to DNA damage increased in parallel. The results provide a new basis for detecting the action of alkylating mutagens on human lymphocytes in vitro or in vivo. (26 refs)

- 79-6467 Idiopathic Paraproteinemia--A Consequence of an Age-related Deficiency in the T Immune System.

Three-Stage Development--A Hypothesis. (Eng) Radl, J. (Inst. Experimental Gerontology TNO, Rijswijk, Netherlands). *Clin Immunol Immunopathol* 14(2): 251-255; 1979.

On the basis of information gained from recent experiments with an animal model of idiopathic paraproteinemia (the aging C57BL mouse), the following stages were hypothesized to occur in the development of this disease. (1) During aging, involution of the thymus and a genetically determined selective decline in certain T-cell populations lead to an impairment of the T-cell functions. The extent and the progression of these changes may be influenced by some extrinsic factors, such as environment, chronic antigenic stimulation, and virus infection. (2) Consequently, cooperation with and control of B cells by the T cells becomes impaired. Restriction of heterogeneity of the immune response and excessive clonal expansions with an overshoot production of homogeneous immunoglobulins-antibodies appear as a result of this imbalance in the immune system network. (3) The repeated mono- or oligoclonal expansions result in a higher probability for either spontaneous or virus-induced mutation of the regulatory genes within a given B-cell clone. In this way, monoclonal proliferation and paraprotein production would continue, even without antigenic stimulation. This intrinsic defect in cell regulation is, however, different from that seen in B-cell malignancies. (28 refs)

- 79-6468 Requirement of Parental T Lymphocytes for the In Vitro Induction of F₁ Hybrid Anti-parent Cytotoxicity. (Eng) Nakamura, I. (Dept. Pathology, State Univ. New York at Buffalo, 232 Farber Hall, Buffalo, NY 14214); Cudkowicz, G. *Eur J Immunol* 9(5): 371-379; 1979.

A model is described in which the induction of primary F₁ anti-parent cell-mediated lympholysis (CML) required the presence of a subpopulation of T lymphocytes, as judged by the lack of induction following T-cell depletion of parental cells by (1) separation on nylon wool columns, (2) treatment with anti-thymocyte-1.2 antiserum and complement, (3) treatment of donor mice with rabbit anti-mouse thymocyte serum, or (4) congenital absence of the thymus in nu/nu donors. The parental T lymphocytes required were relatively mature, as indicated by their resistance to cortisone, persistence after adult thymectomy, and sensitivity to xenogeneic antithymocyte antiserum. T-depleted cell populations retained their ability to induce allogeneic CML. Parental lymphoma cells, spleen cells stimulated by mitogens for T or B lymphocytes, normal cells of central and peripheral lymphoid organs, and peritoneal exudate cells all served to a varying extent as targets for anti-parent cytotoxic effectors (CTL), but there was no close correlation with their ability to serve as stimulators. Spleen or peritoneal exudate cells of athymic mice also served as "antigenic" targets for specific F₁ anti-parent CTL, but they failed to induce the response. Thus, the role of parental T cells in the induction of F₁ anti-parent cytotoxicity was not that of bearing the "antigen." It is concluded that irradiated parental T lymphocytes provide back-stimulation to F₁ hybrid responders, either directly or indirectly via the activation of macrophagelike cells. Under certain circumstances, however, the requirement for parental T cells can be circumvented. (23 refs)

- 79-6469 The Pathology and Homing of a Transplantable Murine B Cell Leukemia (BCL₁). (Eng) Warnke, R. A. (Lab. Experimental Oncology, Dept. Pathology, Stanford Univ., Sch. Medicine, Stanford, CA 94305); Slavin, S.; Coffman, R. L.; Butcher, E. C.; Knapp, M. R.; Strober, S.; Weissman, I. L. *J Immunol* 123(3): 1181-1188; 1979.

The pathology and early and late homing patterns of a spontaneous B cell leukemia (BCL₁) that arose in a BALB/c mouse are described. The most striking gross finding in the original leukemic mouse was massive enlargement of the spleen. Frozen sections stained for κ and λ -light chains showed a homogenous population of λ -bearing B lymphocytes in the white pulp of the spleen including the periarteriolar T cell domains. Five minutes after the iv injection of 5×10^7 or 2.5×10^7 labeled BCL₁ cells, large numbers of labeled cells were present throughout the pulmonary interstitium of BALB/c mice, and small numbers were present in the marginal zones of the spleen. Eighteen hours after injection, a large number of labeled cells were in the spleen, the majority in the marginal zones and in the red pulp; moderate numbers also occurred in the white pulp. Both the number and distribution of cells within the liver were similar at 5 min and 18 hr. The thymus was devoid of labeled cells. In additional mice given 5×10^6 unlabeled BCL₁ cells iv, leukemic infiltrates were not detected until 35 days after injection. Tissues observed grossly, microscopically, and with immunofluorescent staining in the two mice examined at that time were similar to those observed in the original leukemic mouse. It is concluded that this unusual murine B cell neoplasm is a lymphoma with a striking predilection for the spleen and that the other organs, including bone marrow and peripheral blood, are secondarily involved. (24 refs)

- 79-6470 In Vitro Immune Response of Human Peripheral Lymphocytes. IV. Specific Induction of Human Suppressor T Cells by an Antiserum to the T Leukemia Cell Line HSB. (Eng) Hirano, T. (Third Dept. Internal Medicine, Osaka Univ. Medical Sch., Fukushima-ku, Osaka, 553, Japan); Kishimoto, T.; Kuritani, T.; Muraguchi, A.; Yamamura, Y.; Ralph, P.; Good, R. A. *J Immunol* 123(3): 1133-1140; 1979.

An antiserum to the human T leukemic cell line, HSB, absorbed with the autologous B cell line, SB, was tested for complement (C)-mediated cytotoxicity against a variety of human hematopoietic cell lines. T lymphocyte lines HSB and CEM were strongly positive, and line 45 was weakly positive. T lines SKW3 and MOLT-4, five B cell lines (VM, DAUDI, SB, 1788, and BM), and three lines from non-T acute lymphoblastic leukemia (NALL-1), histiocytic lymphoma (U937), and myeloid leukemia (K562) origin were negative. In six normal donors, cytotoxicity of the absorbed antiserum (dHSB) ranged from 23% to 56% of T cells killed at 1:20 dilution. Treatment of purified peripheral blood lymphocyte (PBL) T cells with dHSB and C had no specific effect on their mitogenic responses to phytohemagglutinin (PHA) and concanavalin A (Con A), but partially inhibited mixed lymphocyte culture (MLC) reactions. dHSB and C had no effect on helper T cells or B lymphocytes in pokeweed mitogen (PWM)-induced immunoglobulin production. When dHSB was present during the 7-day culture for PWM-induced immunoglobulin production, there was complete suppression of both IgG and IgM production at a concentration of 1:400. T cells pretreated with dHSB for 3 days and washed were capable of inhibiting immunoglobulin production by normal PBL at ratios <1:100. dHSB-treated B cells had no effect on PWM induction of immunoglobulins. The results show that the dHSB serum does not recognize antigen(s) expressed on the surface on helper T cells and those T cells responding to PHA and Con A, but does recognize T cells responding in MLC and

suppressor T cells in PWM-induced immunoglobulin production. The results further demonstrate that dHSB-treated T cells secrete a soluble factor that suppresses immunoglobulin production by PWM-stimulated PBL. (41 refs)

- 79-6471 Characterization of a Spontaneous Murine B Cell Leukemia (BCL₁). II. Tumor Cell Proliferation and IgM Secretion After Stimulation by LPS. (Eng) Knapp, M. R. (Howard Hughes Medical Inst. Lab., Stanford Univ. Medical Center, Stanford, CA 94305); Severinson-Gronowicz, E.; Schroder, J.; Strober, S. *J Immunol* 123(3): 1000-1006; 1979.

The susceptibility of tumor cells from a spontaneous BALB/c B lymphocyte leukemia (BCL₁) to activation by the polyclonal B cell activator lipopolysaccharide (LPS) was examined. The kinetics of increased [³H]thymidine incorporation by BCL₁ tumor cells after in vitro stimulation with LPS differed from those of normal BALB/c spleen cells. Normal cells showed a peak proliferation on day 3 of culture, while LPS-activated cells showed a peak on day 1. The response to LPS by both cell types showed only a minor dependence on mitogen concentration over a range of 10-500 μ g/ml. The tumor cells responded optimally when cultured at 2.5×10^6 /ml; the response was enhanced in the presence of 5×10^{-5} M 2-mercaptoethanol. Tumor cells from the spleen, but not those from the peripheral blood, could be induced by LPS to secrete IgM. Karyotype analysis of dividing LPS-activated BCL₁ cells showed that the tumor cells themselves proliferated in response to LPS. Immunoprecipitation showed that the light chains on secreted IgM molecules were the λ isotype, which is further evidence that the tumor cells, and not some residual normal B lymphocytes (which secrete IgM bearing both κ and λ light chains), were responding to LPS stimulation. (29 refs)

- 79-6472 Characterization of a Spontaneous Murine B Cell Leukemia (BCL₁). I. Cell Surface Expression of IgM, IgD, Ia, and FcR. (Eng) Knapp, M. R. (Howard Hughes Medical Inst. Lab., Stanford Univ. Medical Center, Stanford, CA 94305); Jones, P. P.; Black, S. J.; Vitetta, E. S.; Slavin, S.; Strober, S. *J Immunol* 123(3): 992-999; 1979.

The surface marker expression of a spontaneous BALB/c B lymphocyte leukemia (BCL₁) was examined. The tumor cells bore surface immunoglobulins that included both μ - and δ -chains associated with the γ light chain. The presence of IgD with BALB/c (Ig^b) allotypic determinants was demonstrated on the surface of tumor cells growing in BAB/14 (Ig^b) animals, demonstrating the endogenous production of IgD by BCL₁ cells. Alloantigens coded for within the murine H-2 complex, including H-2D, H-2K, and I-region products, were identified on the tumor cells. Although normal B lymphocytes are thought to express products coded for within both I-A and I-E subregions, the BCL₁ expressed only normal amounts of I-E subregion products. In addition, H-2 and Ia antigens revealed by 2-dimensional gel electrophoresis exhibited an abnormal pattern of post-translational modifications. The Fc, but not the complement receptor (CR), was present on the surface of tumor cells. The presence of several B cell surface markers suggests that BCL₁ is derived from the B lymphocyte lineage. Since surface IgD and Ia antigens are first seen on mouse cells around the time of birth, after which they are found on most B lymphocytes, the present findings suggest that the BCL₁ tumor represents a later differentiative stage than murine B lymphocyte tumors previously described. The absence of CR may be explained by the immaturity of the BCL₁ cells, the restriction of cells to a CR-negative subpopulation, or to loss of a differentiated function by this cell line. (41 refs)

- 79-6473 Aggressive Biologic Behavior of Basal- and Squamous-Cell Cancers in Patients with Chronic Lymphocytic Leukemia or Chronic Lymphocytic Lymphoma. (Eng) Weimar, V. M. (209 Converse Drive, Jacksonville, NC 28540); Ceilley, R. I.; Goeken, J. A. *J Dermatol Surg Oncol* 5(8): 609-614; 1979.

The aggressive behavior of basal- and squamous-cell carcinomas (BCC and SCC, respectively) in seven patients with chronic lymphocytic leukemia (CLL) or lymphocytic lymphoma (LL) is reported. SCC was first diagnosed 6 yr after the diagnosis of CLL in a 51-yr-old white man, at the same time as CLL in an 80-yr-old man, 2 yr after CLL in a 61-yr-old white man, and 2 yr after LL in a 63-yr-old white man. BCC was first diagnosed 8 yr after diagnosis of CLL in an 88-yr-old white woman, 8 yr after diagnosis of CLL in an 82-yr-old white man, and 6 yr before LL in a 66-yr-old white woman. All patients had normal absolute numbers of T lymphocytes, but the percentage of T cells was decreased in the patients with CLL. The number and percentage of B cells was decreased in two patients with CLL. None of the patients reacted to id tests with common antigens, and they could not be sensitized to dinitrochlorobenzene. The age at onset of the cutaneous cancers was similar to that in the general population, and the cancers were all on sun-exposed skin. However, the incidence of multiple skin cancers was higher (57%) than in the general population (16%), and the incidence of SCC relative to BCC was higher (3:2) than in the general population (1:4). All patients with SCC developed metastases. The data indicate that BCC and SCC may be more aggressive and more resistant to treatment in some patients with CLL or LL. Actinic keratosis in such patients should be treated early and vigorously to prevent transformation into carcinomas, and all BCCs and SCCs larger than 1 cm should be treated by microscopically controlled excision. (25 refs)

- 79-6474 A Chemotactic Inhibitor Produced by Blast Cells and Present in the Serum of a Patient with Acute Lymphoblastic Leukemia. (Eng) Blumenfeld, W. (Dept. Medicine, Univ. California at Los Angeles, Center Health Sciences, Los Angeles, CA 90024); Territo, M. *Blood* 54(2): 412-420; 1979.

A chemotactic factor inhibitor (CFI) found in the serum of a 26-yr-old man with acute lymphoblastic leukemia was characterized. The factor was heat-labile, and it was active against complement-dependent chemotactic factors and against the chemotactic factor produced by *Escherichia coli*. This suggested that the defective chemotaxis in the patient resulted from increased amounts of CFI. Normal sera and sera from seven other patients with acute leukemia also demonstrated heat-labile inhibitory activity against complement-dependent chemotactic factors, but not against the *E. coli*-derived chemotactic factor. Supernatants from cultured lymphoblasts of the patient also possessed CFI activity similar in character to that found in his serum. It is suggested that in vivo, the lymphoblasts were responsible for the chemotactic defect observed in his serum, presumably by manufacturing and releasing a CFI. (12 refs)

- 79-6475 Cultured Human Leukemic Non-T/Non-B Lymphoblasts and Their Stimulating Capacity in "One-Way" Mixed Lymphocyte Reaction. Suggestive Evidence for Early T-Cell or B-Cell Precursors. (Eng) Han, T. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Dadey, B.; Minowada, J. *Cancer* 44(1): 136-140; 1979.

The stimulating capacity of cultured leukemia lymphoblasts from five non-T/non-B cell lines in one-way mixed lymphocyte reac-

tions was studied and compared with the stimulating capacities of cultured leukemic T and B lymphoblasts. Lymphoblasts from three non-T/non-B cell lines (NALL-1, NALM-6, and NALM-16) consistently exerted strong stimulation on allogeneic lymphocytes, whereas those from two other non-T/non-B lines (REH and KM-3) consistently failed to stimulate. Leukemic B lymphoid cells from four cell lines consistently excited a strong stimulation, whereas those from four T lymphoid cell lines consistently failed to stimulate allogeneic normal lymphocytes. The data support the hypothesis that leukemic non-T/non-B cells that possess stimulating ability may represent less differentiated leukemic B lymphoid cells (pre-B cells) and that leukemic non-T/non-B cells that possess no stimulating activity may represent pre-T cells. (25 refs)

- 79-6476 In Vitro Induction of Cytotoxic Effector Cells Against Human Neoplasms. I. Sensitization Conditions and Effect of Cryopreservation on the Induction and Expression of Cytotoxic Responses to Allogeneic Leukemia Cells. (Eng) Kedar, E. (Lautenberg Center General and Tumor Immunology, Hadassah Medical Sch., Hebrew Univ., Jerusalem, Israel); Raanan, Z.; Kafka, I.; Holland, J. F.; Bekesi, G. J.; Weiss, D. W. *J Immunol Methods* 28(3/4): 303-319; 1979.

The parameters that govern the in vitro sensitization of peripheral blood lymphocytes (PBL) against freshly obtained human leukemia cells were defined using PBL from normal human donors that were sensitized in vitro against allogeneic human acute myelocytic leukemia (AML) cells by a unidirectional mixed lymphocyte-tumor cell culture (MLTC) technique. The cytotoxic responsiveness of the sensitized lymphocytes, determined in vitro by the ^{51}Cr -release assay, varied among individual lymphocyte donors and was generally dependent on the sensitization culture conditions. Induction of cytotoxic effector cells was augmented appreciably by adding minute amounts of the immunopotentiating agent methanol-extracted residue of BCG to the cultures. Responding lymphocytes and stimulating leukemia cells cryopreserved for several weeks in liquid nitrogen were as effective as fresh cells in generating effector lymphocytes; the cytotoxic capacity of previously sensitized lymphocytes was retained by cryopreservation. (42 refs)

- 79-6477 Loss of H-2* Gene Product(s) from an AKR Spontaneous Leukemia. (Eng) Schmidt, W. (Dept. Immunology, London Hosp. Medical Coll., Turner St., London E1 2AD, England); Atfield, G.; Festenstein, H. *Immunogenetics* 8(4): 311-321; 1979.

The H-2 antigenic specificities on the AKR (H-2*) spontaneous leukemia K36 were studied using serological absorption and immunochemical techniques. Of five anti-H-2.23 alloantisera against the private specificity of the H-2* haplotype, two (C23 and WSF7) were cytotoxic for the K36 tumor. Absorption of serum C23 with B10.A cells completely removed activity against B10.A only, whereas absorption with C3H.OH and K36.16 cells removed activity only against C3H.OH and K36.16. Thus, anti-H-2.23 and not anti-H-2.23 activity in the C23 serum appeared to be responsible for the reactions against C3H.OH and tumor. Absorption of serum WSF7 with B10.A removed all reactivity against all test cells, whereas absorption with C3H.OH and K36 removed only reactivity against C3H.OH and K36.16. The concordant reactivity of WSF7 with all three test cells appeared to be directed against an H-2 public specificity common to all and not anti-H-2.23. Cytotoxicity and absorption studies were conducted with sera

directed against the private and public specificities of the *H-2^k* haplotype. The results suggested that not only the private specificities of the *H-2K^k* gene, but also the public specificities that are known to be associated and present on the same molecule, are either missing or have greatly reduced expression on the K36 tumor cell. The *H-2D^k* gene products were present as expected. Non-cytotoxic antisera D23.b did not immunoprecipitate K36 glycoprotein in the mol wt range of histocompatibility antigens on electrophoresis. A precipitate in the 45,000-dalton range obtained by unabsorbed anti-*H-2.23* serum appeared not to be *H-2*. The results confirm the absence of the *H-2K^k* gene product from the cell surface of K36 and from detergent-solubilized tumor cells. (39 refs)

- 79-6478 Immunopotentiality Against the L1210 Leukemia by Pyran Copolymer and Crude Tumor Antigen. (Eng) Mohr, S. J. (Div. Urology, Univ. Colorado Medical Center, Denver, CO 80220); Chirigos, M. A. *Prog Cancer Res Ther* 7: 415-426; 1978.

The immunopotentiating properties of pyran in the L1210 tumor system were studied using adult male B6D2F₁, DBA/2, and CD2F₁ mice. Animals vaccinated with irradiated L1210 cells plus pyran copolymer showed significantly prolonged survival times after challenge with live L1210 cells, compared with controls vaccinated only with irradiated tumor cells. Significant immunity was present as early as 24 hr after pyran-vaccine treatment, and the protection afforded by this treatment appeared to be systemic. All three strains of mice responded well, although the hemisynthetic CD2F₁ mice showed the greatest response. The potentiating effect of pyran was also seen with other immunoadjuvants, such as BCG and glucan, and with all of the newly synthesized preparations of divinyl ether-maleic anhydride. However, the ability to potentiate immunity was not necessarily shared with all compounds possessing similar physical properties to pyran. When animals with established L1210 leukemia were treated with pyran, the drug proved to be only weakly therapeutic. However, pyran-vaccine treatment given 3 days after cytoreductive chemotherapy for established leukemia increased the survival time with chemotherapy alone by another 25%. (11 refs)

- 79-6479 Induction of Tumor Resistance in Mice By L1210 Leukemia Cells Persistently Infected with HVJ (Sendai Virus). (Eng) Takeyama, H. (Sloan-Kettering Inst. Cancer Res., New York, NY); Kawashima, K.; Yamada, K.; Ito, Y. *Gann* 70(4): 493-501; 1979.

The ability of L1210 leukemia cells persistently infected with HVJ (Sendai virus) to induce resistance against L1210 leukemia was studied using various inbred and hybrid mouse strains. L1210 cells infected with wild-type HVJ (L1210/c-HVJ-w cells) did not proliferate in growth medium and were damaged by HVJ-w. A paramyxovirus (HVJ-pi) from baby hamster kidney cells persistently infected with HVJ had no cytopathic effect on L1210/c cells, and L1210/c-HVJ-pi cells grew well in growth medium. Serially subcultured L1210/c-HVJ-pi cells carried viral antigens of HVJ. L1210/c-HVJ-w cells inoculated ip into DBA/2 or BDF₁ mice did not grow, whereas viable L1210/c-HVJ-pi cells showed a low degree of transplantability in normal syngeneic mice. The percentage of viral antigen-positive cells appeared to be inversely correlated with the growth of L1210/c-HVJ-pi cells in vivo. More than 90% of BDF₁ or CDF₁ mice immunized with 10⁵ L1210/c-HVJ-pi cells were protected against subsequent ip challenge with 10⁵ intact L1210/c cells. HVJ-pi or homogenized L1210/c cells offered no such protection. In the mice preimmunized with L1210/c-

HVJ-pi cells that died after tumor cell challenge, tumor development was markedly delayed. The induction of immune resistance was more prominent in (C57BL/6 x DBA/2)F₁ or (BALB/c x DBA/2)F₁ mice than in DBA/2 mice. Preimmunization with L1210/c-HVJ-pi cells did not protect against challenge with tumor other than L1210. (27 refs)

- 79-6480 Cell-Surface Characteristics of Hairy Cell Leukemia in Seven Patients. (Eng) Yanovich, S. (Dept. Tumor Immunology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA 02115); Marks, S. M.; Rosenthal, D. S.; Moloney, W. C.; Schlossman, S. F. *Cancer* 43(6): 2348-2351; 1979.

Surface marker studies were made of circulating peripheral blood hairy cells from seven patients with hairy cell leukemia (HCL). None of the patients had received chemotherapy. Sensitive analytic techniques, including specific antisera and the Fluorescence Activated Cell Sorter (FACS-1), were used to further define the abnormal cells. Four different antisera were used to investigate the cell-surface characteristics of these patients: (1) anti-p23,30, an antiserum reactive with B cells and a subset of monocytes; (2) anti-311, which reacts only with T cells; (3) pepsin-digested anti-F(ab')₂, which reacts only with B cells; and pepsin-digested antilysozyme, which is reactive with monocytes and myeloid cells but not with B or T cells. In all cases, strong reactivity was observed with anti-p23,30 and anti-F(ab')₂, but no reactivity was observed with anti-311. Five of the patients were reactive with antilysozyme in a pattern similar to that of normal monocytes. Furthermore, when cells were separated according to binding to anti-p23,30, anti-F(ab')₂, and anti-lysozyme and, in two cases, according to cell size, the majority of reactivity and large cells were "hairy" when examined under the microscope. In contrast, the small and nonreactive (dull cells) had the appearance of normal mature lymphocytes. Thus, the data support the view that HCL cells bear, in most cases, B-cell and monocytic membrane markers. (29 refs)

- 79-6481 Lipopolysaccharide Responsiveness of Malignant Lymphoid Cells in a Patient with Hairy Cell Leukemia. (Eng) Tatsumi, E. (First Div. Internal Medicine, Faculty Medicine, Kyoto Univ., Kyoto, Japan); Domae, N.; Takiuchi, Y.; Sawada, H.; Shirakawa, S.; Uchino, H. *Blood* 54(2): 524-529; 1979.

A positive response to lipopolysaccharide (LPS) by the malignant lymphoid cells of a 52-yr-old Japanese man with hairy cell leukemia (HCL) is reported. In medium supplemented with either fetal calf serum or human plasma, the cells showed a remarkable degree of stimulation by LPS 026:B6 and LPS 055:B5. The cells of normal individuals and individuals with other forms of leukemia showed a much lower degree of stimulation. The LPS-stimulated cells of the HCL patient showed a broadened and slightly basophilic cytoplasm, a dilated endoplasmic reticulum, and an increase in the number and the size of mitochondria; they were clearly distinct from unstimulated cells. (26 refs)

- 79-6482 Immunological Studies in Hairy Cell Leukemia. (Eng) Davey, F. R. (State Univ. New York, Upstate Medical Center, 750 E. Adams St., Syracuse, NY 13210); Dock, N. L.; Terzian, J.; Bala, R.; Gottlieb, A. J. *Arch Pathol Lab Med* 103(9): 433-436; 1979.

The results of cytochemical and immunological studies of tissues and mononuclear cell suspensions from 10 patients with hairy cell

leukemia are presented. In all cases studied, tartrate-resistant acid phosphatase was noted within the cytoplasm of the hairy cells (HC's). In two-thirds of the cases, α -naphthyl acetate esterase was observed in the HC's. In addition, HC's did not form spontaneous rosettes with sheep RBC. A variable number of HC's displayed complement receptors. The nonspecific binding of conjugated immunoglobulin (Ig) to HC's probably reflected the presence of a high concentration of Fc receptors on the surface of the HC's. In three cases, the conjugated Ig reacted predominantly to one light chain, suggesting the presence of a monoclonal Ig. In four of six cases, mononuclear cell suspensions of HC's demonstrated latex phagocytosis. In one case, HC's displayed resynthesis of surface membrane Ig, the presence of B-cell antigen, and phagocytosis of latex. These findings suggest that HC's are distinctive and contain properties of both B lymphocytes and monocytes. (32 refs)

- 79-6483 Definition of a Unique Cell Surface Antigen of Mouse Leukemia RL[Female]1 by Cell-mediated Cytotoxicity. (Eng) Nakayama, E. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Shiku, H.; Takahashi, T.; Oettgen, H. F.; Old, L. J. *Proc Natl Acad Sci USA* 76(7): 3486-3490; 1979.

The specificity of the cytotoxic T-cell response to the x-ray-induced BALB/c leukemia RL[female]1 [RL(f)1] was investigated. RL(f)1 is strongly immunogenic for (BALB/c x C57BL/6)F₁ mice. Transplants of RL(f)1 regressed after initial growth, and after tumor regression mice could resist repeated inocula of 10⁷ RL(f)1 cells. Spleen cells from immunized mice after in vitro stimulation with RL(f)1 were cytotoxic for RL(f)1 cells in 3-hr ⁵¹Cr assays. Pretreatment of immune spleen cells with Thy-1, Lyt-2, or Lyt-3 antisera and complement eliminated cytotoxic activity, indicating that effector cells for RL(f)1 lysis are T cells. Tests with other target cells showed little or no cytotoxicity. Analysis of the specificity of T-cell killing of RL(f)1 by competitive inhibition assays with unlabeled cells indicated that only RL(f)1 could inhibit killing. Other BALB/c tumors (13 x-ray or murine leukemia virus-induced leukemias and 3 myelomas) failed to inhibit lysis of RL(f)1. Various alloantisera and heteroantisera were tested for their capacity to block lytic activity in the absence of added complement. H-2^d antisera and Lyt-2 and -3 antisera blocked lysis, the latter at the level of the effector cell. Antisera to other cell-surface alloantigens, murine leukemia virus-related antigens, and immunoglobulins did not block RL(f)1 lysis. Thus, T cells from mice immunized against RL(f)1 recognize an individually distinct or unique antigen that does not appear to be related to any of the serologically defined cell-surface determinants of RL(f)1. In its restriction to a single leukemia, the RL(f)1 antigen resembles the individually distinct antigens of chemically induced tumors and other tumor types of rodents. (23 refs)

- 79-6484 Tumor Metastases and Cell-mediated Immunity in a Model System in DBA/2 Mice. VI. Similar Specificity Patterns of Protective Anti-Tumor Immunity In Vivo and of Cytolytic T Cells In Vitro. (Eng) Bosslet, K. (Institut für Immunologie und Genetik, Deutschen Krebsforschungszentrum, Heidelberg, W. Germany); Schirmacher, V.; Shantz, G. *Int J Cancer* 24(3): 303-313; 1979.

In an attempt to analyze mechanisms of immunity against tumor metastases, protective antitumor immunity in vivo was compared with cytotoxic T-cell activity in vitro in a well-defined syngeneic tumor model system. The system consisted of a chemically induced murine lymphoma (Eb) with little or no metastatic potential and its

spontaneous variant (ESb) with pronounced metastatic properties. Tumor protection experiments revealed the presence of tumor-associated transplantation antigens (TATAs) on both Eb and ESb tumor cells. TATAs of Eb and ESb were found to be distinct and did not cross react. One of several unrelated tumors, however, RL(male)1, expressed TATAs which cross-reacted with those of Eb. Protective immunity against the nonmetastasizing tumor was much stronger than that against the metastasizing variant. Striking differences were found in the optimal procedures for induction of in vivo immunity to each tumor. Tumor-specific cytotoxic T lymphocytes (CTLs) were obtained after sensitization in vivo with viable tumor cells and restimulation in vitro for 4-5 days with mitomycin-C-treated autologous tumor cells. Both anti-Eb and anti-ESb CTLs showed high cytolytic activity in a 4-hr ⁵¹Cr release assay against the autologous tumor lines. The target antigens recognized by these cells were similar to the TATAs as defined in the protection experiments (ie, distinct and non-cross-reactive). Only one of 14 unrelated syngeneic and allogeneic tumors expressed a target antigen which cross-reacted with that of Eb. This tumor was the radiation-induced BALB/c lymphoma RL(male)1 which also cross reacted at the level of the TATAs. The correlations between protective immunity obtained in vivo and cytolytic T cells induced in vitro suggest that cytolytic T cells can recognize TATAs and may thus play an important role in the establishment of protective immunity. (40 refs)

- 79-6485 Morphological Changes During Late Ontogenesis in Offspring of Mice with Induced Graft-vs-Host Reaction. (Rus) Fedosov, E. A. (Dept. Microbiology, Medical Inst., Smolensk, USSR); Zarudin, V. V. *Biull Eksp Biol Med* 88(7): 111-114; 1979.

A hypothesis concerning the existence of a direct relationship between disturbances of the immune system in mothers and the development of pathological changes of the immune system in their offspring was tested. Pregnant (CBA x C57BL/6)F₁ mice were inoculated with lymph node and spleen cells from normal C57BL/6 mice, and pregnant CBA mice were inoculated with cells (unspecified) from C57BL/6 donors immunized with spleen cells of CBA mice. The offspring of females with an induced graft-vs-host reaction were followed for 2 yr. Various malignancies were recorded in 18/62 of these offspring (compared with 1/24 controls). There were 11 lymphocytic neoplasms and 7 reticulocellular neoplasms. Tumorigenesis was associated with marked splenomegaly (up to 2-3 g) in eight mice and increased thymus wt (up to 90 mg, vs 20-30-mg in controls) in three mice. (17 refs)

- 79-6486 Opposing Tumorigenic and Immunogenic Properties of the In Vitro and the In Vivo Sublines of Moloney Induced Tumor. (Eng) Devens, B. (Dept. Immunology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Galili, N.; Naor, D.; Klein, E. *Proc Leukocyte Cult Conf* (12): 707-714; 1979.

The tumorigenic and immunogenic properties of the in vitro (YAC-1) and in vivo (YAC) sublines of a Moloney virus-induced tumor carried in A mice were studied. Injection of one YAC cell into the peritoneal cavity of a normal syngeneic mouse resulted in death within about 7 wk. In contrast to the YAC tumor, the YAC-1 tumor showed remarkable immunogenic properties. The results of a co-target competition experiment indicated that the antigenic structure of the YAC tumor is different from that of the YAC-1 tumor, and that YAC-1 priming stimulates separate populations of effector cells to the two targets YAC and YAC-1. Spleen cells from A/J mice primed with the allogeneic Rauscher virus-induced RBL5

tumor of C57BL/6 mice cultivated for 6 days in vitro could generate cytotoxic responses against YAC and YAC-1 tumors. Spleen cells from A mice injected with YAC-1 or RBL5 cells could also generate a cytotoxic response against RBL5. The YAC tumor could not stimulate antitumor-reactive cells in A mice. It is concluded that the suppressor cells can discriminate between RBL5-primed cells and YAC-1-primed cells and exert their suppressive effect on cells that possess specificity to YAC-1 only. The antitumor reactivity induced by YAC-1 tumor could confer partial but significant antitumor resistance on A/J mice injected with low doses of viable tumor. (8 refs)

- 79-6487 Angioimmunoblastic Lymphadenopathy. Evolution to a Burkitt-like Lymphoma. (Eng) Mazur, E. M. (Dept Medicine, Yale Univ. Sch. Medicine, LC1 802, 333 Cedar St., New Haven, CT 06510); Lovett, D. H.; Enriquez, R. E.; Breg, W. R.; Papac, R. J. *Am J Med* 67(2): 317-324; 1979.

A primitive lymphoid neoplasm characterized by generalized lymphadenopathy, hepatosplenomegaly, and bone marrow and peripheral blood infiltration by lymphoid blast cells developed in a 64-yr-old woman with angioimmunoblastic lymphadenopathy of 1.5 yr duration. The blast cells demonstrated a high nuclear-cytoplasmic ratio, a deeply basophilic cytoplasm, and prominent cytoplasmic vacuoles, features similar to those described in both immunoblastic and Burkitt's cell leukemias. The clinical course resembled that of Burkitt's lymphoma, with markedly elevated serum lactate dehydrogenase levels that paralleled disease activity, hyperuricemia before therapy, and marked tumor sensitivity to the administration of cyclophosphamide, vincristine, cytosine arabinoside and prednisone that resulted in acute hyperkalemia, hyperphosphatemia and hypocalcemia. The patient died 3.5 mo after malignant transformation with leukemic meningitis. Cytogenetic studies of circulating blast cells revealed a distinctive translocation from the long arm of chromosome 8 to the long arm of chromosome 14 [46XX, t(8q-; 14q+)]. This karyotype has been correlated with Burkitt's lymphoma. The blast cells possessed no demonstrable B- or T-cell surface markers, nor did they transform to a continuous cell line in tissue culture. Antibody to Epstein-Barr viral capsid antigen was minimally increased at a titer of 1:80. No antibody to Epstein-Barr early antigen was present. This patient demonstrates the clinical, pathologic, and cytogenetic overlap among Burkitt's cell and immunoblastic leukemias and lymphomas. These disease processes appear to be part of a continuum in which this patient represents an intermediate form. (44 refs)

- 79-6488 Suppression of Cell-mediated Tumor Cell Lysis and Complement-induced Cytotoxicity by Trypan Blue. (Eng) Scornik, J. C. (Res. Service, Veterans Admin. Medical Center, Gainesville, FL 32602); Ruiz, P.; Hoffman, E. M. *J Immunol* 123(3): 1278-1284; 1979.

The effects of trypan blue (TB) on cell-mediated lysis (CML) of Ehrlich ascites tumor (EAT) cells and complement-induced cytotoxicity were studied. Different forms of CMC were suppressed in the presence of TB. The systems affected included antibody-coated EAT cells lysed by normal and *Corynebacterium parvum*-stimulated mouse peritoneal cells, and allogeneic targets lysed by immune effector cells. The inhibition, which was measured in a 4-hr ^{51}Cr -release assay, was reversible and did not occur in the presence of 30% fetal calf serum or albumin. Binding between effector and target cells through Fc receptors was unaffected, and lysis of allogeneic cells was inhibited at the lytic step rather than at the binding step. In contrast, lysis of sensitized RBCs was not inhibited by TB, suggesting that the lysis of these

targets may not involve the steps involved in tumor cell lysis. TB blocked the function of antibody before binding to target cells and also suppressed complement-induced cytolysis. Most individual complement components were susceptible to the inhibitory action of TB. These results reveal an affinity of TB for proteins that may be responsible for many of its biological actions. (30 refs)

- 79-6489 Lymphocyte Surface Membrane Immunoglobulin in Myeloma. I. M315-bearing T Lymphocytes in Mice with MOPC-315. (Eng) Gebel, H. M. (Dept. Pathology, Div. Biology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO 63110); Hoover, R. G.; Lynch, R. G. *J Immunol* 123(3): 1110-1116; 1979.

Studies were conducted to determine whether the small M315 antibody-bearing mononuclear cells, which account for more than one-third of the circulating mononuclear cells in mice with 315/+ tumors, are myeloma cells or host lymphocytes. 315/+ is derived from the MOPC-315 plasmacytoma and differentiates from M315 producing, nonsecreting, lymphocytoid cells to large M315 secreting plasmacytoid cells. Experiments in CBF₁ mice demonstrated that the circulating M315-bearing cells were of F₁, rather than tumor origin. Serologic and ultrastructural studies demonstrated that the cells were post-thymic T lymphocytes. After proteolytic removal, surface M315 was re-expressed in vitro by 315/+ cells, but not by T cells. M315-bearing T cells accounted for 0% to 4% of circulating mononuclear cells in mice with 315/P, a variant of MOPC-315 in which all cells synthesize M315, but only 2% of the cells are secretory. There was no obvious relationship between the frequency of M315 bearing lymphocytes and development of the humoral immunodeficiency that accompanies myeloma. These findings (1) identify an association between high levels of M315 secretion and development of M315-bearing T cells; (2) favor the view that M315 is acquired, rather than produced by host T cells; and (3) raise the possibility that T cells with IgA-Fc receptors may be increased in mice with 315/+ tumors. (29 refs)

- 79-6490 Binding Constants of NZB Myeloma Antidextran for Dextran and Isomaltose Oligosaccharides Determined by Affinity Electrophoresis. (Eng) Sugii, S. (Dept. Microbiology, Columbia Univ., Coll. Physicians and Surgeons, New York, NY 10032); Takeo, K.; Kabat, E. A. *J Immunol* 123(3): 1162-1168; 1979.

The association constants of two NZB mouse myeloma antidextran, PC3858 and PC3936, were measured by affinity electrophoresis. With linear dextrans or with those with a low degree of branching, the association constants of dextrans ranged from 2.7×10^3 to 5.4×10^4 ml/g for PC3858 and from 1.3×10^4 to 2.6×10^5 ml/g for PC3936. Completely linear α -(1 \rightarrow 6)-linked dextrans, LD7 and D3, showed high affinities for the two NZB antidextran. The association constants of oligosaccharides (K_a) increased as the number of α -(1 \rightarrow 6)-linked glycosyl residues increased. Isomaltoheptaose (IM7) showed the highest K_a (1.9×10^4 M $^{-1}$ for PC3858 and 1.63×10^4 M $^{-1}$ for PC3936). Pullulan and glycogen showed very weak affinity for PC3936, but they did not react at all with PC3858. These findings indicate that NZB myeloma antidextran, PC3858 and PC3936, are specific for internal chains of α -(1 \rightarrow 6)-linked dextrans. (21 refs)

- 79-6491 Cloning of Immunoglobulin Kappa Light Chain Genes from Mouse Liver and Myeloma MOPC 173. (Eng) Steinmetz, M. (Institut fur Physiologische Chemie,

Physikalische Biochemie und Zellbiologie, Universität München, München, W. Germany; Zachau, H. G.; Mach, B. *Nucleic Acids Res* 6(10): 3213-3229; 1979.

The organization of the κ -chain constant-region gene was compared in DNA from an immunoglobulin-producing mouse myeloma (MOPC 173) and from BALB/c mouse liver. In situ hybridization using the Southern blotting technique revealed constant-region gene-containing EcoRI-DNA fragments of 14 and 20 kilobases (kb) in the myeloma tissue, whereas one EcoRI-DNA fragment with a length of 15 kb was found in liver DNA. After enrichment by RPC-5 chromatography and preparative electrophoresis, the 14-kb fragment from MOPC 173 DNA and the 15-kb fragment from liver DNA were cloned in the bacteriophage λ vector Charon 4A using in vitro packaging. Extensive characterization of the two fragments by restriction endonuclease mapping, in situ hybridization, and electron microscopy (R-loop and heteroduplex) showed that both contain the constant-region but no MOPC 173 variable-region gene. Both fragments are homologous over a length of 12.5 kb, including the constant region, but they differ from one another starting about 2.7 kb from the 5' end of the constant-region gene. This indicates that the 14-kb EcoRI-DNA fragment from the myeloma tissue clearly resulted from somatic DNA rearrangement, although it does not seem to carry the MOPC 173 variable-region gene. These observations suggest that somatic DNA rearrangement of immunoglobulin light-chain genes can involve both homologous chromosomes. (36 refs)

79-6492 Similarity of Casein- and Endotoxin-induced, Myeloma-associated and Aged SJL/J Amyloid in Various Strains of Mice. (Eng) Baumal, R. (Dept. Pathology, Univ. Toronto, Medical Sciences Bldg., Toronto, Ontario M5S 1A8, Canada). *Int Arch Allergy Appl Immunol* 59(1): 20-27; 1979.

Myeloma-associated amyloids of Balb/C mice, amyloids arising spontaneously in aged SJL/J mice, and amyloids induced by casein or endotoxin were compared. None of the amyloid preparations reacted with various anti-Ig antisera, but anti-casein and anti-myeloma amyloid antisera reacted with all three forms of amyloid. Analysis of the casein- and endotoxin-induced amyloids by electrophoresis revealed similar peaks of mol wt 12,000 in both cases. Similar results were obtained with the spontaneous amyloids, and it was concluded that all three forms existed as non-covalently bonded dimers. All three forms were also susceptible to potassium permanganate and oxalic acid, with or without trypsin digestion, as assessed by incubation of formalin-fixed, paraffin-embedded sections of amyloidotic spleens with these reagents prior to Congo-red staining. All forms of amyloid yielded similar peptide maps following digestion with trypsin and resolution on a Dowex column. Since the casein-induced murine amyloid resembles the nonimmunoglobulin form of human amyloid, it is concluded that an immunoglobulin form in mice has yet to be characterized. (20 refs)

79-6493 Immunologically Nonspecific Enhancement of Artificial Lung Metastases in Tumor-bearing Mice. (Eng) Ando, K. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX 77030); Hunter, N.; Peters, L. J. *Cancer Immunol Immunother* 6(3): 151-156; 1979.

Enhancement of tumor growth in the lungs of tumor-bearing male C₃Hf/Bu mice inoculated iv with cells of the same syngeneic

transplantable fibrosarcoma (NFSA) was studied. Compared with untreated controls, mice bearing tumors for 14 days, but not less, developed significantly more lung colonies ($p < 0.01$). The number of lung colonies depended on the number of tumor cells injected, and spontaneous metastases were not the major reason for the enhancement. Mice showing enhanced lung tumor growth showed concomitant resistance to im tumor challenge. The tumor-induced enhancement disappeared shortly after surgical removal of the original tumors and was decreased relative to tumor-bearing controls even after subsequent iv tumor challenge. Whole-body γ irradiation (600 rad) and treatment of tumor-bearing mice with *Corynebacterium parvum* prior to iv tumor challenge prevented the enhancement phenomenon. Tumor-induced enhancement of lung colonies was also prevented by T-cell depletion (thymectomy followed by whole-body irradiation and bone-marrow reconstitution), but was not affected by adult thymectomy alone. Enhancement was not tumor-specific in that mice bearing another fibrosarcoma (FSA), which does not cross react immunologically with NFSA, also showed enhancement when challenged iv with NFSA. (8 refs)

79-6494 Cell-mediated Immune Response to Syngeneic UV-induced Tumors. IV. The Presence of I-A and I-E Subregion-coded Antigens on the Accessory Cell Required for the In Vitro Differentiation of Cytotoxic T Lymphocytes. (Eng) Woodward, J. G. (Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, UT 84132); Daynes, R. A. *J Immunol* 123(3): 1227-1231; 1979.

The I-subregion-defined antigens present on the accessory cell required for the generation of antisynthetic tumor immunity were studied in mice, using the UV-induced C3H fibrosarcoma, RD-87. The removal of both anti-I-A and anti-I-E activity from anti-Iak serum by absorption was required to deplete cytotoxic activity against the accessory cells. Antisera specific for the A, B, and J subregions of the *k* haplotype as well as an antiserum specific for the J, E, or E, C subregions detected specificities present on both draining lymph node (DLN) accessory cells and splenic accessory cells. It was not possible to reduce accessory cell function with antisera specific for only J subregion-coded determinants. When antisera containing only the known specificities mapping in I-A or I-E were used, accessory cell function was eliminated from DLN cultures. When antisera specific for only Ia.7 of the *K* haplotype were used, accessory cell function was also eliminated. The data suggest that the accessory cell required for the in vitro generation of a tumor immune response expresses antigens that code in both the I-A and I-E subregions of the major histocompatibility complex. Ia.7 may be the important serologic specificity coding in the I-G subregion. Both A- and E-subregion-coded determinants appear to be expressed on the same population of accessory cells. (21 refs)

79-6495 Specific Triggering of Macrophage Accumulation at the Site of Secondary Tumor Challenge in Mice with Concomitant Tumor Immunity. (Eng) Hopper, K. E. (Kolling Inst. Medical Res., Royal North Shore Hosp. of Sydney, St. Leonards, New South Wales 2065, Australia); Nelson, D. S. *Cell Immunol* 47(1): 163-169; 1979.

The peritoneal cellular response to tumor challenge was studied in CBA/J mice bearing sc isografts of syngeneic 3-methylcholanthrene-induced fibrosarcoma C-4 or C-15. In mice bearing C-4 isografts for 7 days and challenged ip with C-4, but not in those challenged with C-15, there was a significant increase in peritoneal macrophages. The macrophage counts in mice bearing

C-4 tumors for 14 days were significantly raised after ip challenge with either C-4 or C-15. Peritoneal macrophage numbers were also significantly elevated in normal mice injected ip with C-4 cells plus peritoneal cells from mice bearing C-4 tumor for 7 days as compared with normal mice injected with C-4 cells only or C-4 cells plus peritoneal cells from non-tumor-bearing mice. The new population of peritoneal cells were young monocyte-derived macrophages as determined by their morphology, position, sedimentation velocity profiles, chemotaxis, and labeling in vivo following [^3H]thymidine injection. The data suggest that the expression of immunity to some methylcholanthrene-induced fibrosarcomas involves reactions akin to delayed-type hypersensitivity in which an immunologically specific reaction triggers the delivery of nonspecific effector cells to the site of tumor challenge. (7 refs)

- 79-6496 **Passive Enhancement of Mouse Tumor Allografts by Alloantibodies is Fc-Dependent.** (Eng) De Waal, R. M. (Dept. Pathology, Univ. Nijmegen, Geert Grooteplein Zuid 24, 6500 HB Nijmegen, Netherlands); Cornelissen, I. M.; Capel, P. J.; Koene, R. A. *J Immunol* 123(3): 1353-1355; 1979.

The role of the Fc and F(ab')₂ antibody fragments in the enhancement of mouse tumor allograft growth following the injection of alloantisera against donor transplantation antigens in tumor-bearing recipients was investigated. The tumor used was a mouse fibrosarcoma induced in a B10.D2 female mouse by sc injection of methylcholanthrene. A suspension of tumor cells (2×10^6) was injected intracutaneously in female B6AF₁ recipients, and tumor growth was followed macroscopically. Enhancement of tumor growth was induced by ip injections of alloantiserum on days 0, 2, and 4 after transplantation. No macroscopically detectable tumor growth occurred without treatment with an enhancing antiserum. Dose-response studies with intact IgG showed that the threshold dose for induction of enhancement by IgG was 300-960 μg . F(ab')₂ in a dose of 2,200 μg was ineffective. Multiple daily injections of F(ab')₂ (1,000 $\mu\text{g} \times 2$ on day 0; $\times 3$ on day 1, 2, 3, 4, and 5) were also ineffective (0/10 mice with growing tumors). These data indicate that administration of F(ab')₂ fragments of alloantibodies to recipients of mouse tumor allografts does not result in enhancement of tumor growth. This finding is contrary to other reports, which may be explained by contamination with undigested IgG. It is concluded that the Fc part of the alloantibody molecule is required for the induction of enhancement of mouse tumor allografts. (21 refs)

- 79-6497 **Competition Between Foetal Tissue and Macrophage-dependent Natural Tumour Resistance.** (Eng) Keller, R. (Immunobiology Res. Group, Inst. Medical Microbiology, Univ. Zurich, Zurich, Switzerland). *Br J Cancer* 40(3): 417-423; 1979.

Competition between fetal liver cells and macrophage-dependent natural cytotoxicity was studied in vitro, and the enhancement of tumor growth by irradiated fetal liver cells was demonstrated. Prolonged interaction between *Corynebacterium parvum*-induced adherent phagocytic peritoneal cells and syngeneic or xenogeneic tumor targets consistently produced marked cytotoxicity. In the presence of irradiated (2,000 rad) liver cells from 14- to 16-day-old syngeneic (DA rat) or allogeneic (Zbz:Car) embryos, this spontaneous cytotoxicity against various target cells was blocked in a dose-dependent manner. Irradiated liver cells from adult donors manifested no such competition with tumor targets. The ability of irradiated liver cells to compete with tumor targets such as DMBA-

12, Py-12, or P-815 cells was progressively and rapidly lost after birth as indicated with assays using liver cells obtained on day 1, 3, or 5 after birth. Inoculation of 7,12-dimethylbenz(a)anthracene (DMBA)-induced syngeneic ascites tumor cells (DMBA-12: 10^7 cells, ip) into DA rats consistently resulted in progressive tumor growth. The inoculation of 10^6 - 10^7 irradiated syngeneic (or allogeneic) fetal liver cells 1 day before tumor cell challenge promoted tumor growth. Irradiated liver cells from adult donors had no such effect. Tumor growth promotion by fetal liver cells was consistently marked in rats >9 mo old, but was less pronounced in younger rats. Tumor growth was markedly enhanced when irradiated fetal cells were administered either shortly before or after tumor cell inoculation. These findings are consistent with a role for nonspecific immunity in tumor resistance and underline the critical nature of the initial phase of tumor nidation. (24 refs)

- 79-6498 **Recognition of RSV-induced Tumor Cells in Syngeneic Mice and Semisyngeneic Reciprocal Hybrid Mice.** (Eng) Yoshida, T. O. (Dept. Microbiology, Hamamatsu Univ. Sch. Medicine, Handa-cho 3600, Hamamatsu 431-31, Japan); Haraguchi, S.; Miyamoto, H.; Matsuo, T. *Gann Monogr Cancer Res* 23: 201-212; 1979.

The immunogenetic control of the growth of virus nonproducing tumor cells induced by Schmidt-Ruppin strain of Rous sarcoma virus in inbred mice was investigated in syngeneic, F₁ hybrid semisyngeneic and H-2 identical allogeneic mice. The data on recognition (blastogenesis) in vitro and the resistance (transplantability, survival period, and injection) of F₁ hybrid semisyngeneic mice against BALB/cCr sarcoma cells C-SA-1M (derived from male mouse) and C-SA-9F (derived from female mouse) suggested that reciprocal semisyngeneic mice, H-2(d/k), (C \times C3)F₁, (C \times B10BR)F₁; H-2(k/d), (C3 \times C)F₁, (B10BR \times C)F₁; H-2(d/b), CBF₁; H-2(b/d), BCF₁, showed high resistance; H-2(d/a), (C \times B10A)F₁ showed a moderate resistance; and H-2d/d, CDF₁, DCF₁, (C \times B10D2)F₁, (B10D2 \times C)F₁, showed a low resistance. Further evidence in reciprocal F₁ hybrid mice suggested that even if reciprocal semisyngeneic F₁ hybrid mice are the same at gene level, the phenotypic resistance of the mice to the transplantation of parental tumor cells is markedly different. This phenomenon may be related to maternal inheritance. The role of H-Y antigen on the surface of tumor cells in relation to the immunological xenogenization of tumor cells may prove to be a very important factor. (26 refs)

- 79-6499 **Induction of Sarcomas in Nude Mice by Implantation of Syrian Hamster Fetal Cells Exposed In Vitro to Nickel Subsulfide.** (Eng) Costa, M. (Dept. Medical Pharmacology and Toxicology, Texas A&M Univ. Coll. Medicine, College Station, TX 77843); Nye, J. S.; Sunderman, F. W.; Allpass, P. R.; Gondos, B. *Cancer Res* 39(9): 3591-3597; 1979.

Athymic (nude) mice were used to evaluate the tumorigenicity of Syrian hamster fetal cells that had been exposed to nickel subsulfide. In vitro exposure of the cells to $\alpha\text{Ni}_3\text{S}_2$ yielded positive colony assays for morphological transformation. A dose-response relationship was found between the concentration of $\alpha\text{Ni}_3\text{S}_2$ and the incidence of morphological transformation. Exposures to $\alpha\text{Ni}_3\text{S}_2$ induced morphological transformation at concentrations (0.1 or 1.0 $\mu\text{g}/\text{ml}$ culture medium) that did not impair cell plating efficiency. Nickel monosulfide did not induce morphological transformation of the fetal cells under the same conditions. Clones of $\alpha\text{Ni}_3\text{S}_2$ -transformed cells were able to grow in soft agar medium, and they demonstrated increased basal and induced activities of ornithine decarboxylase. Undifferentiated sarcomas

developed in 26/27 nude mice at the site of sc injection of clones of $\alpha\text{Ni}_3\text{S}_2$ -transformed cells. No tumors developed in 19 control nude mice that were given sc injections of nontransformed fetal cells that had not been exposed to $\alpha\text{Ni}_3\text{S}_2$. Thus, fetal cells that undergo transformation following exposure to $\alpha\text{Ni}_3\text{S}_2$ are capable of producing malignant tumors in nude mice. (47 refs)

- 79-6500 Action of Complement in the Lysis of Mouse Sarcoma Cells Sensitized with H-2 alloantibody. (Eng) Reske-Kunz, A. B. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Scheid, M. P.; Abbott, J.; Metakis, L. J.; Polley, M. J.; Boyse, E. A. *Transplantation* 28(2): 149-153; 1979.

Sequential steps in complement binding and activation and their effects on nucleated cell lysis were studied using a modified cytotoxicity assay in which complement components were added in sequence to antibody-sensitized cells. The assay was applied to a model system in which mouse sarcoma cells were sensitized with H-2 alloantibody. The concentration of C1 giving optimal lysis in the nucleated cell system was $50 \mu\text{l}$ per 5×10^6 cells. With iodine-oxidized whole human serum (^{125}I -HS) at 1:40, C4 inhibited the lysis of Meth A cells by H-2 antibody at concentrations $>4 \mu\text{g}$, and max cytolysis was obtained without the addition of C4, indicating that ^{125}I -HS contained enough C4 for optimal lysis. The time of max formation of EAC142 (tmax) in the Meth A system was longer than tmax in the classical reaction sequence in erythrocytolysis, and an approx twofold increase in lytic activity was achieved by incubating sensitized cells complexed with C1 and C4 (TAC14) with ^{125}I -HS or ^{125}I -C2 for 60 min rather than 11 min. ^{125}I -HS in the modified assay was 20-fold more active than guinea pig serum and HS in the conventional assay, and approx 1.5-fold more active than rabbit serum. The activity of ^{125}I -HS was 6.3-fold greater than PO_4 -HS and 4-fold more active than HS when each serum was incubated for its respective tmax. The antiserum-specific lysis of Meth A tumor cells appeared to be mediated to some extent by the alternative pathway alone, and C2-deficient HS appeared to contain heteroantibodies capable of activating the alternative pathway and leading to cytolysis. The data may suggest that multiple complement-mediated functional lesions are necessary for immune lysis of nucleated cells. (26 refs)

- 79-6501 Age-related and Thymus-dependent Rejection of Adenovirus 2-transformed Cell Tumors in the Syrian Hamster. (Eng) Cook, J. L. (Natl. Inst. Allergy and Infectious Disease, NIH, Bethesda, MD 20205); Lewis, A. M.; Kirkpatrick, C. H. *Cancer Res* 39(9): 3335-3340; 1979.

The age-related and thymus dependent rejection of adenovirus 2 (Ad2)-transformed cell tumors in Syrian hamsters was investigated. Ad2-transformed hamster cell-induced newborn tumor lines were usually rejected when transplanted sc into 21-day-old syngeneic, weanling hamsters. The tumor-inducing capacity of two of these lines (Ad2HTL3 and Ad2HTL6) was tested in intact and neonatally thymectomized hosts. After sc injection of suspensions prepared from these lines, none of the weanling hamsters developed tumors, but 100% of the newborns and 35.2% of neonatally thymectomized, weanling hamsters developed progressively enlarging neoplasms. The susceptibility of neonatally thymectomized hamsters to tumor challenge was directly related to the degree of immunosuppression observed following thymectomy, as indicated by the amplitude of the in vitro response of blood WBC to concanavalin A. Pretreatment of thymectomized weanlings with syngeneic adult lymphoid cells (ip) resulted in a significant reduction in tumor susceptibility ($p = 0.03$). These findings

suggest that acquisition of resistance to Ad2-transformed cells during the first 21 days of life may be a thymus-dependent cellular immune process. (24 refs)

- 79-6502 Rejection of Tumor Cells In Vitro: Morphological Studies on Killer T Cells and Damaged Tumor Cells. (Eng) Berczi, I. (Dept. Immunology, Faculty Medicine, Univ. Manitoba, Winnipeg, Manitoba, Canada); Kovacs, K.; Horvath, E.; Sehon, A. H. *Int Arch Allergy Appl Immunol* 59(1): 1-12; 1979.

The in vitro destruction of methylcholanthrene-induced guinea pig sarcoma (MC-D) by killer T lymphocytes was studied using light and electron microscopy. Killer lymphoblasts (LBC) usually emerged between days 5 and 7 and destroyed the MC-D monolayer within 48-72 hr. The LBC were extremely mobile and, once all the MC-D cells were killed, floated freely in the supernatant, stopped proliferating, and gradually lost their viability. Some of the LBC remained viable for up to 3 wk, and upon restimulation achieved by adding MC-D target cells, they started to proliferate. The LBC closely resembled antibody-forming plasma cells but lacked the extensive network of rough endoplasmic reticulum (RER) and did not produce immunoglobulin. In MC-D cells with slight LBC-induced injury, dilatation, vesiculation, fragmentation, and degeneration of the RER were the most characteristic findings. In cells with extensive injury, widespread nuclear and cytoplasmic alterations were evident; and many of these cells were fragmented into smaller portions and finally transformed into granular membranous and amorphous debris. Many cells contained mature and immature particles resembling C-type viruses. These particles were detected in both intact and injured cells. It is suggested that the LBC cells are end cells similar to those of B lymphocyte-derived plasma cells and that the virus particles observed became activated during the interaction of LBC with MC-D. (36 refs)

- 79-6503 Immunocytochemical Studies of Human Myeloma Cells by Light and Electron Microscopy. (Eng) Biberfeld, P. (Dept. Pathology, Karolinska Inst., Stockholm, Sweden); Mellstedt, H.; Pettersson, D. *Isr J Med Sci* 15(8): 687-692; 1979.

Monoclonal cells from the blood of myeloma patients were studied using immunocytochemical techniques. The presence of various numbers of lymphoid cells expressing myeloma protein determinants on their surface was consistently demonstrated. The relative number of these surface idiotype-positive cells (sld+) varied from 3%-45% before treatment to 0% or slightly more during remission; during relapse and the terminal stages of the disease, the number increased to up to 60%-70%. The idiotype determinants were of endogenous and monoclonal origin, and they expressed only one type of light chain. In general, the number of cells stainable for intracellular immunoglobulin paralleled the number stainable for myeloma protein. Only 4/15 patients had demonstrable cytoplasmic immunoglobulin in their monoclonal, circulating cells; these myelomas were cytologically the most well differentiated. Both immunocytochemical and ultrastructural observations indicated various morphological types of myeloma cells ranging from lymphoid cytology to definite plasmacytoid differentiation. However, most patients showed some lymphoidlike myeloma cells in their blood. Monitoring the blood levels of idiotype-positive and immunoglobulin-positive cells appears to be a sensitive probe for following the development of human myeloma. (11 refs)

79-6504 Partial Characterization of an Antigen from a Human Myeloma Cell and Its Reactivity with an Anti-myeloma Cell Serum. (Eng) Krueger, R. G. (Lab. Molecular Oncology, Christ Hosp. Inst. Medical Res., 2141 Auburn Ave., Cincinnati, OH 45219); Hilton, P. *Int J Cancer* 24(2): 134-140; 1979.

The antibody specificity of a rabbit antiserum generated to the RPMI 8226 line of human myeloma cells was studied and the antigen was isolated and characterized. In a quantitative semimicro complement fixation assay, the antiserum reacted to a significantly higher titer with RPMI 8226 cells than with RPMI 4098 human lymphocytes or normal human bone marrow cells, particularly after absorption with RPMI 4098 cells. A similar difference in reactivity was noted for cell-free lysates of the three different cell types. Of various solubilization procedures used, deoxycholate treatment of sonicated or freeze-thaw extracts, 3 M KCl, autolysis, and papain digestion solubilized antigens from RPMI 8226 cells that reacted with anti-RPMI 8226 cell serum absorbed with RPMI 4098 cells. The solubilized RPMI 8226 cell antigens did not react with an antiserum to RPMI 4098 cells. Components solubilized from RPMI 4098 cells by similar procedures did not react with the absorbed anti-RPMI 8226 cell serum to a significant extent. The material solubilized from the RPMI 8226 cells consisted of three proteins with approx mol wts of 66,000, 55,000, and 31,000 daltons, as estimated by acrylamide gel electrophoresis. The results indicate that the RPMI 8226 cell line possesses antigens not found on the RPMI 4098 line, that these antigens can be solubilized, and that they react with an antiserum generated to intact RPMI 8226 cells. (17 refs)

79-6505 Receptor Sites for Complement and for Immune Complexes on Human Nonhemopoietic Tumor Cells. (Eng) Biran, H. (Dept. Development Therapeutics, M. D. Anderson Hosp. and Tumor Inst., Univ. Texas System Cancer Center, 6723 Bertner Ave., Houston, TX 77030); Mavligit, G. M.; Moake, J. L. *Cancer* 44(1): 131-135; 1979.

Primary cultures of tumor cells derived from 11 untreated nonhematopoietic cancer patients were reacted with specifically coated sheep erythrocytes (E's). Rosette formation between tumor and indicator cells was assessed. Eight of the primary cultures reacted positively with both IgG-coated (EA_{I_gG}) and with IgM-human complement-coated (EA_{I_gM}C or EA_{I_gM}C 4,3) sheep E's. EA_{I_gG} rosette formation in positive cultures ranged from 25% to 85%, and for EA_{I_gM}C/EA_{I_gM}C 4,3, reactivity ranged between 22% and 95%. Rosette formation with E (uncoated) and EA_{I_gM} was negligible. These findings suggest that human nonhematopoietic tumor cells may carry on their surface receptor sites for an IgG component of immune complexes and for human complement. These receptor sites may be important in the host-tumor relationship. (33 refs)

79-6506 Histocompatibility Antigens in Patients with Hepatocellular Carcinoma and Their Relationship to Chronic Hepatitis B Virus Infection in These Patients. (Eng) Kew, M. C. (Dept. Medicine, Univ. Witwatersrand Medical Sch., Hospital Hill, Johannesburg, South Africa 2001); Gear, A. J.; Baumgarten, I.; Dusheiko, G. M.; Maier, G. *Gastroenterology* 77(3): 537-539; 1979.

Forty histocompatibility antigens (HLA) of 102 South African blacks with histologically confirmed hepatocellular carcinoma (HCC) were compared with those of 208 healthy controls using a standard two-stage lymphocyte microcytotoxicity assay. The fre-

quencies of only three antigens (HLA-A1, HLA-A W36, and HLA-B7) differed significantly between HCC patients and controls, and these differences were not significant when the data were corrected for the total number of antigens tested. The frequency of HLA antigens did not differ significantly between 50 patients positive for hepatitis B surface antigen (HBsAg) and 50 HBsAg-negative patients. Of 92 patients tested, 88% were positive for antibody against hepatitis B core antigen (anti-HBc). The pattern of HLA antigens in these patients did not appear to differ significantly from that in anti-HBc-negative patients. The data show no evidence of a genetic predisposition to either hepatocellular carcinoma or to chronic hepatitis B surface antigenemia in patients with HCC. (14 refs)

79-6507 Activity of Syngeneic Complement for Revealing Antibody-induced Cytotoxicity Against a Rat Hepatoma. (Eng) Price, M. R. (Cancer Res. Campaign Lab., Univ. Nottingham, University Park, Nottingham NG7 2RD, England); Hoffken, K.; Baldwin, R. W. *Transplantation* 28(2): 140-143; 1979.

The cytotoxicity of tumor-bearer serum against a transplanted aminoazodye-induced rat hepatoma (D23) was studied using normal WAB/Not rat serum as the source of complement and a short-term ⁵¹Cr release test. Hepatoma D23-bearer serum displayed complement-dependent cytotoxicity for hepatoma D23 cells, and both normal and tumor-bearer rat serum contained the appropriate and sufficient complement components required to mediate antibody lysis in vitro. Treatment of rats with normal rat serum or heat-inactivated normal rat serum following an sc challenge of 10³ D23 cells had no effect on the incidence of sc tumors. Similar results were obtained when the D23 cells were injected into the peritoneal cavity. However, when unheated sera were used in similar tests and an incubation of 2 hr was performed prior to injection, the cytotoxic action of the tumor-bearer serum was demonstrated. These findings indicate that tumor-specific complement-dependent cytotoxicity of tumor-bearer serum against syngeneic rat hepatoma cells occurs when rat serum is used as the source of complement. That the tumor-bearing rat contains both antibody and complement sufficient for tumor lysis suggests that this may impose some immunological control upon the survival of cells released from the developing tumor. (21 refs)

79-6508 The Nude Mouse as a Tissue Amplifier for Studies of Experimental and Human Pancreas Cancer. (Eng) Fitzgerald, P. J. (Dept. Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY); Sharkey, F. E.; Fogh, J.; Varricchio, F.; Cubilla, A.; Pour, P. In: *The Nude Mouse in Experimental and Clinical Research*. Fogh, J.; Giovanella, B. C., eds. (New York: Academic Press): 502 pp.; 267-279; 1978.

The use of the nude mouse as a tissue amplifier for studies of experimental and human pancreatic cancer was studied. A human duct cell adenocarcinoma, a nitrosamine-induced hamster duct adenocarcinoma, and a rat azaserine-induced acinar cell carcinoma were transplanted into nude mice and maintained over a few generations. Of the three tumors, the acinar cell tumor grew the fastest. With regard to the human pancreatic tumors, the shorter the time between removal of the tissue and its transplantation, the greater the chance of growth in the nude mouse. Three of five rat tumors grew in the nude mouse, and the hamster tumor grew in 1/4 mice. All three tumor types retained the general morphological appearance of the original tumor, although there was a tendency for the adenocarcinomas to become more glandular. The

original hamster tumor did not appear to be malignant, but the mouse transplant was malignant. The presence of a relatively high concentration of amylase in the acinar cell cancer and its absence in the duct cell cancers were in keeping with their origins. The observed relative decrease in the H1^o histone in the rat acinar cell carcinoma was associated with the focal anaplasia of this tumor. The nude mouse provides a means whereby large amounts of tumor tissue can be harvested for biochemical, immunologic, and morphologic studies. (13 refs)

- 79-6509 Temperature-dependent Alteration in Immunogenicity of Tumor-associated Transplantation Antigen Monitored via Paraformaldehyde Fixation. (Eng) Oikawa, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ., Sch. Medicine, Sapporo 060, Japan); Gotohda, E.; Austin, F. C.; Takeichi, N.; Boone, C. W. *Cancer Res* 39(9): 3519-3523; 1979.

Paraformaldehyde-fixed mKSA tumor cells, a simian virus 40-transformed BALB/c kidney cell line, were shown to retain tumor-associated transplantation antigen (TATA) activity to a degree comparable to that of x-ray-inactivated tumor cells under the optimal conditions of 1% paraformaldehyde for 30 min at 37 C. Unexpectedly, the TATA activity of cells fixed below 10 C was greatly reduced. This temperature effect was reversible. TATA activity was restored if the cells were returned to 37 C before fixation. Fixation at all temperatures for >2 hr or at paraformaldehyde concentrations >1% also caused a decrease in immunogenicity. In the Winn assay, spleen cells from mice immunized with tumor cells fixed at 37 C were able to neutralize tumor growth more effectively than those from mice immunized with cells fixed at 0 C. Immunization with paraformaldehyde-fixed tumor cells was completely specific. Mice immunized with an antigenically unrelated tumor were not rendered immune to tumor challenge. Fixed tumor cells could be stored for at least 1 mo without loss of TATA activity. (30 refs)

- 79-6510 HLA System in Wilms' Tumor of the Kidneys and in Neuroblastoma. (Cze) Abrahamova, J. (Onkologicka klinika, Fakulta vseobecneho lekarstvi KU, U nemocnice 2, 128 08 Prague 2, Czechoslovakia); Majsky, A.; Koutecky, J. *Cesk Pediatr* 34(5): 268-270; 1979.

Twenty-three HLA antigens of loci A and B were detected in lymphocytes of 46 children (24 boys and men, 12 girls and women; aged 1-24 yr) with Wilms' tumor and in those of 20 patients (9 boys and men, 11 girls and women, aged 1-24 yr) with neuroblastoma. Three hundred and one healthy subjects served as controls. The frequencies of HLA-A1 and A9 were increased in the patients with Wilms' tumor (45.65% and 36.95%, respectively, vs 28.24% and 19.27% in controls). The incidence of the HLA-B₁₃ and Bw₂₁ antigens was increased in patients with neuroblastoma (25% and 15%, respectively), compared with controls (8.98% and 4.65%, respectively). (5 refs)

- 79-6511 The Immune Reactivity of Patients with Cancer of the Esophagus. (Ita) Ancona, E. (Istituto di Patologia Chirurgica III, Universita degli Studi di Padova, Padua, Italy); Amadori, G.; Ninfo, V.; Bardini, R.; Semenzato, G.; Gasparotto, G.; Peracchia, A. *Minerva Med* 70(23): 2311-2320; 1979.

The immune reactivity of 50 patients with various stages of epidermoid cancer of the esophagus was evaluated in several tests. In general, erythrocyte (E)-rosette formation and the lymphocyte response to phytohemagglutinin were significantly depressed in the

patients compared with controls. However, the responses of individual patients varied. (56 refs)

- 79-6512 Carcinoembryonic Antigen (CEA) in the Gastric Mucosa After Partial Gastrectomy. (Eng) Janunger, K. G. (Dept. Surgery, Univ. Hosp., Umea, Sweden); Lindgren, J.; Sipponen, P.; Domellof, L. *Scand J Gastroenterol* 14(5): 555-560; 1979.

Carcinoembryonic antigen (CEA) was studied by the three-layer bridge immunoperoxidase technique in gastric biopsy specimens taken from 49 patients, 13-20 yr after partial gastrectomy. Routine histological examination revealed various degrees of chronic atrophic gastritis in all patients. A positive CEA reaction was found in 6/9 patients with malignant or premalignant mucosal changes and in 4/40 without these changes. In two cases of carcinoma the biopsies revealed a positive CEA reaction. Of 4 patients with carcinoma diagnosed 1-2 yr after the first examination the initial nonmalignant biopsies were CEA-positive in one case. All biopsies from mucosa with severe dysplasia and adenomatous polyps were CEA-positive. Four patients without malignant or premalignant changes in the gastric mucosa had CEA-positive biopsies. No carcinoma has been found in these patients at re-examinations after 1 yr. The results indicate that the occurrence of immunohistochemically detectable CEA in the gastric mucosa may be associated with malignant transformation. (32 refs)

- 79-6513 Lysis of Allogeneic Tissue Cultured Colorectal Cancer Cells by Blood Group Isoantibody in Normal Human Serum. (Eng) Cohen, A. M. (Cox Cancer Center, Massachusetts General Hosp., Boston, MA 02114); Wood, W. C. *J Surg Res* 27(1): 1-7; 1979.

Established tissue culture colorectal cancer lines were evaluated for the presence of cell-surface blood group isoantigen activity. Four tumor cell lines obtained from donors of blood groups A or AB were used as targets in complement-dependent cytotoxic antibody and mixed hemagglutination assays. The presence of cell-surface isoantigen A-like activity was demonstrated on these lines by a micromixed hemagglutination reaction. The majority of sera obtained from type O normal donors was cytotoxic. The B sera were less frequently reactive. Despite the presence of isoantigen B-like activity on one cell line, sera from normal A donors were not reactive. Human serum was an adequate source of complement in these reactions. The specificity of these reactions was confirmed by RBC absorption experiments. Blood group isoantigen activity represents another area of potential confusion in the study of human tumor cell-surface antigens using allogeneic colorectal cancer cells. (28 refs)

- 79-6514 Analysis of the Expression of H-2 and H-2-linked Antigens on Mammary Tumor Cells. (Eng) Snoek, M. (Div. Genetics, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Amsterdam, Netherlands); Demant, P. *Int J Cancer* 24(2): 165-167; 1979.

The products of the recently discovered H-2L locus were expressed on BALB/c mammary tumor cells and behaved as histocompatibility antigens, in contrast to the products of H-2-linked loci (Qa loci), which did not influence the acceptance or rejection of tumor transplants in syngeneic and allogeneic recipients. (19 refs)

- 79-6515 Lack of Relationship of Transplantation Immunogenicity in C3H/He Mammary Carcinomas,

with Lymphoid Hyperplasia and Radiation-induced Growth Enhancement. (Eng) Vaage, J. (Dept. Cancer Therapy Development, Pondsby Hosp., Walpole, MA 02081). *Cancer Immunol Immunother* 6(3): 185-189; 1979.

Lymphoid hyperplasia during the progressive growth of three syngeneic C3H/He mammary carcinomas (immunogenic MC31-1B, growth-stimulating MC31-5B, and neutral MC31-7B) in female C3H/He mice was studied. After sc implantation, all three mammary carcinomas (MC) caused lymphoid hyperplasia in the hosts, as did sc pieces of autochthonous or syngeneic normal liver or kidney; sterile styrofoam implants had no effect. All three MC grew significantly better in irradiated (300 rad total-body irradiation 2 days before challenge) mice than in normal hosts. The spleen was consistently smaller in irradiated than in nonirradiated hosts. On the basis of these observations, it is concluded that neither lymphoid hyperplasia in normal hosts nor growth enhancement in immunosuppressed hosts is a reliable in vivo test for tumor-specific transplantation immunogens. (12 refs)

79-6516 Inhibition of Lymphocyte Function in Rats Fed High-Fat Diets. (Eng) Kollmorgen, G. M. (Cancer Res. Program, Oklahoma Medical Res. Foundation, Oklahoma City, OK 73104); Sansing, W. A.; Lehman, A. A.; Fischer, G.; Longley, R. E.; Alexander, S. S.; King, M. M.; McCay, P. B. *Cancer Res* 39(9): 3458-3462; 1979.

The effects of high-fat diets [20 g polyunsaturated fat (PSF) or saturated fat (SF) per 100 g of feed] on lymphocyte function were studied in female outbred Sprague-Dawley rats. 7,12-Dimethylbenz(a)anthracene (DMBA) was given via a stomach tube as a single 10-mg dose. The mammary tumor incidence after DMBA was significantly lower in rats on the SF diet than in those on the PSF diet or the control low-fat (LF) diet. Lymphocytes from rats on the LF diet showed a comparable blastogenic response when grown in autologous serum, allogeneic serum from rats on the LF diet (ASLF), or horse serum. A significantly lower response was observed when these lymphocytes were grown in serum from rats on the PSF diet. Lymphocytes from rats on the PSF diet showed a significantly lower blastogenic response in serum when compared with those from rats on the LF diet. Lymphocytes from the PSF rats showed a significantly higher response when grown in horse serum or ASLF than when grown in serum or allogeneic serum from PSF rats. Serum deficiency was not responsible for these observations, and it was concluded that blastogenesis was inhibited by one or more serum factors. Lipoprotein-free serum from rats on the LF diet did not inhibit the blastogenic response of LF lymphocytes, but significant inhibition was associated with the lipoprotein fraction. In contrast, lipoprotein-free serum from rats on the PSF diet did inhibit the blastogenic response; and very severe inhibition was observed when the lipoprotein fraction from this serum was evaluated. (32 refs)

79-6517 Immunity to the T1699 Murine Mammary Tumor. II. Thymic Influence on the In Situ Inflammatory Response, Metastatic Growth and Invasiveness. (Eng) Parthenais, E. (Transplantation Lab., Univ. Helsinki, Haartmaninkatu 3A, SF 00290 Helsinki 29, Finland); Haskill, S. *J Immunol* 123(3): 1334-1338; 1979.

The influence of cellular vs humoral immunity on the syngeneic mammary adenocarcinoma T1699 was investigated using adult thymectomized, lethally irradiated, bone-marrow-repopulated (ATXBM) and nonthymectomized, irradiated-repopulated, (CXBM) DBA/2 female mice. Tumors were induced by sc injection of

T1699 tissue culture tumor cells in the abdominal area. Median survival time for ATXBM tumor bearers was 38 days, compared with 86 and 91 days for CXBM and nonirradiated tumor bearers, respectively. At 14 days after tumor cell injection, the number of in situ monocyte-macrophages, eosinophils, and lymphocytes was markedly reduced, whereas neutrophils were more numerous in the ATXBM hosts than in tumors from CXBM or nonirradiated mice. Dissemination and metastatic growth occurred at a high frequency in the ATXBM hosts (23/29) but not at all in the CXBM hosts (0/32); one pulmonary metastatic nodule was observed in 1/41 nonirradiated tumor bearers. Invasion from the primary subcutaneous site through the peritoneal wall and seeding of the peritoneal cavity occurred in the ATXBM mice but not in the CXBM or nonirradiated tumor bearers. These studies suggest distinct roles for the two immunoglobulin subclasses that localize within the T1699 tumor. It appears that the thymus-independent IgG2b antibody promotes the in situ inflammatory response through an immediate hypersensitivity reaction and that the thymus-dependent IgG2a antibody, which supports antibody-dependent cellular cytotoxic reactions, restrains tumor growth at both the primary and metastatic sites. (29 refs)

79-6518 Immunity to the T1699 Murine Mammary Tumor. I. Thymic Influence and Long-Term Effect of Irradiation on the Humoral Response. (Eng) Parthenais, E. (Transplantation Lab., Univ. Helsinki, Haartmaninkatu 3A, SF 00290 Helsinki 29, Finland); Haskill, S. *J Immunol* 123(3): 1329-1333; 1979.

Immediate hypersensitivity reactions, macrophage-mediated antibody-dependent cellular cytotoxicity (ADCC), and membrane-fluorescent tumor-directed immunoglobulins were assessed in adult-thymectomized, lethally irradiated, bone-marrow-repopulated (ATXBM), syngeneic DBA/2 female mice. ATXBM animals bearing T1699 mammary tumors in the subcutaneous abdominal area displayed normal immediate but not delayed hypersensitivity reactions (DHR) to 3 M potassium chloride T1699 extracts injected into the footpad. Sera from ATXBM tumor bearers passively transferred immediate hypersensitivity but did not support tumor-specific macrophage-mediated ADCC reactions. Macrophage-mediated ADCC antibody synthesis was greatly reduced in the nonthymectomized lethally-irradiated bone-marrow-repopulated (CXBM) animals when compared to nonirradiated tumor bearers. The CXBM mice showed normal T cell function as measured by allograft rejection, antibody response to sheep RBC, and DHR to T1699 antigens. At 14 days after tumor induction, normal levels of IgG2b were found in both ATXBM and CXBM tumor bearer sera by indirect membrane fluorescence. Depressed levels of all other antibody classes tested (IgA, IgM, IgG1, IgG2a, and IgG3) were observed in both the ATXBM and CXBM tumor bearers. These results indicate that IgG2b antibody production in response to T1699 syngeneic tumor antigens is thymus-dependent and suggest that this antibody is the mediator of immediate hypersensitivity. The results also indicate that IgG2a and IgM antibody synthesis is not only thymus-dependent but also sensitive to the long-term effects of irradiation. (16 refs)

See also:

*(Rev.): 79-6009, 79-6038, 79-6039, 79-6081, 79-6082, 79-6083, 79-6084, 79-6085, 79-6086, 79-6087, 79-6092.

*(Chem.): 79-6133, 79-6161, 79-6267, 79-6270, 79-6297, 79-6298, 79-6310, 79-6311.

*(Phys.): 79-6363.

*(Viral): 79-6383, 79-6403, 79-6405, 79-6408, 79-6419, 79-6426, 79-6429, 79-6446, 79-6448.

*(Path.): 79-6524, 79-6525.

- 79-6519 Malignant Transformation of a Warthin Tumor: Case Report, Review of the Literature, and Discussion of Pathology. (Eng) Caldwell, E. H. (Div. Plastic Surgery, Strong Memorial Hosp., 601 Elmwood Ave., Box 661, Rochester, NY 14642); Armiger, W. G.; McDonald, H. M. *Ann Plast Surg* 3(2): 177-181; 1979.

A case history is presented of a 33-yr-old man in whom a benign papillary cystadenoma lymphomatosum (PCL; Warthin's tumor) underwent malignant transformation without previous radiation therapy. The tumor was excised, and histological and electron microscopic studies confirmed that the malignancy originated from the PCL. A review of the literature indicated that several reports of malignant transformation of PCL have been published, but only three have been convincingly proved. These three confirmed cases were all in patients with a previous history of radiation to the neck. In the present case, light microscopy revealed malignant undifferentiated carcinoma in which a single focus of benign PCL was found. Electron microscopy showed malignant epithelial cells of two types: polyhedral or cylindrical cells with dark and light nuclei corresponding to the dark and light cells of the benign PCL; however, the tumor cells had larger nucleoli, a higher nucleus to cytoplasm ratio, and more prominent cytoplasmic rough endoplasmic reticulum and microfilaments. It is believed that this case represents the first report of proved malignant transformation of PCL in a patient with no previous history of radiotherapy. (11 refs)

- 79-6520 Cutaneous Acute Myeloblastic Leukaemia and Squamous Cell Carcinoma. (Eng) Harrison, P. V. (Dept. Dermatology, General Infirmary, Leeds LS2 3EX, England); Rowell, N. R. *Br J Dermatol* 101(2): 207-210; 1979.

The development of a cutaneous deposit of leukemic cells within a squamous cell carcinoma as the first presentation of acute myeloblastic leukemia in a 77-yr-old man is reported. The lesion was excised, ultimate healing was excellent, and the initial response to chemotherapy was excellent, but the patient died from bronchopneumonia. A blood film was characteristic of acute myeloblastic leukemia (85% blast cells), and a bone marrow examination and the postmortem examination confirmed the diagnosis. The fibrinogen level and kaolin cephalin clotting time were reduced, and the prothrombin time, thrombin time, and fibrin degradation products were elevated. Histologic examination of the skin showed a deposit of acute myeloblastic leukemia cells within a poorly differentiated keratinizing squamous cell carcinoma. (23 refs)

- 79-6521 Lymphoepithelioid Cell Malignant Lymphoma (Lennert). (Eng) Bednar, B. (Hlava's 1st Pathological-Anatomical Institute, Faculty Medicine, Charles Univ., Albertov 2039, 128 00 Prague, Czechoslovakia). *Virchows Arch [Pathol Anat]* 382(3): 313-322; 1979.

A prospective study was made of lymphoepithelioid cell malignant lymphoma (LCMM). Typical epithelioid cell formations were found in 175/500 cases of various types of Hodgkin's disease. No distinctive behavior was found in cases with epithelioid structures.

A more detailed study was made of a further series of 23 LCMM's marked by focal nuclear atypicality in their epithelioid cell granulomas. The atypicality destroyed the basic neoplastic structure of the lymph node in many cases, necessitating further biopsy. In this series, not only Hodgkin's disease (7 cases), but also some non-Hodgkin's type malignant lymphomas (3 immunoblastomas, 3 immunocytomas, and 2 T-cell lymphoblastomas) were found. In 6/23 cases, only a tentative diagnosis of LCMM could be made. The epithelioid granulomatous reaction tended to disappear gradually in all cases and was apparently a secondary phenomenon. The cause of the epithelioid cell atypia was not evident, although it proved to be an important diagnostic feature identifying an independent form of LCMM. The subsequent development of this lesion suggested a mildly pleiomorphic, highly malignant lymphoma that might be of B- or T-cell origin. (10 refs)

- 79-6522 Chromosomes and Causation of Human Cancer and Leukemia. XXXII. Unusual Features of Ph⁺-positive Acute Myeloblastic Leukemia (AML), Including a Review of the Literature. (Eng) Abe, S. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Sandberg, A. A. *Cancer* 43(6): 2352-2364; 1979.

Five cases of Philadelphia chromosome (Ph⁺)-positive acute myeloblastic leukemia (AML) are described. In all cases, a Ph⁺ chromosome was shown by banding techniques to be due to a translocation between chromosomes 9 and 22. Cases 2 and 4 had more than one Ph⁺, with evidence of only one Ph⁺ translocation accompanying other chromosome abnormalities. Two cases represented an unusual pattern of appearance and disappearance of the Ph⁺-positive clone during their clinical courses. Case 2 was originally Ph⁺-positive (46,XY,Ph⁺), but 2 mo before expiration, the Ph⁺-positive clone was completely replaced by a newly developed Ph⁺-negative clone with an abnormal chromosome 21 (46,XY,21q+). Case 3, primarily Ph⁺-negative, developed a Ph⁺-positive clone among the previously karyotypically normal cells 1 mo before death. The Ph⁺-positive AML cases are discussed in relation to (1) the genesis and significance of the Ph⁺-positive clone, (2) differentiation from the blastic phase of chronic myelocytic leukemia, and (3) general experience with Ph⁺-positive acute nonlymphocytic leukemia (ANLL). Ph⁺-positive cases of ANLL in the world literature are tabulated. (43 refs)

- 79-6523 A Case of Burkitt's Lymphoma. (Pol) Rupniewska, Z. M. (Klinika Hematologii, Instytut Chorob Wewnętrznych AM, ul. Jaczewskiego 8, 20-950 Lublin, Poland); Korobowicz, E.; Metera, M. *Pol Arch Med Wewn* 61(5): 411-414; 1979.

Burkitt's lymphoma was diagnosed in a 21-yr-old man who had never been in an endemic region. The diagnosis was based on the histological examination of a lymph node, which displayed a characteristic starry sky appearance. In the pleural exudate and in the bone marrow, large cells with strongly basophilic cytoplasm and numerous vacuoles (Burkitt's lymphoma cells) were found. The characteristic chromosome markers (14q⁺ and 8q⁺) were absent. The diagnosis was confirmed at autopsy. (7 refs)

79-6524 Burkitt's Lymphoma: Review of the Literature and Report of Four Cases in Denmark. (Dan) Pallesen, G. (Univ. Inst. Pathology, Univ. Aarhus, Kommunehospitalet, DK-8000 Aarhus C, Denmark); Andersen, H.; Jensen, M. K.; Philip, P.; Hansen, N. E.; Badsberg, E.; Vilholm, H. E. *Ugeskr Laeger* 141(27): 1827-1832; 1979.

The histopathology, clinical manifestations, etiology, immunology, and cytogenetics of Burkitt's lymphoma (BL) are reviewed. In addition, the case reports of four BL patients (3 women and 1 man with a mean age of 19.4 yr) are presented. The disease presented as acute leukemia in two patients. In all four patients, the disease was disseminated and predominantly abdominal, corresponding to Stage IV. All the women had bilateral ovarian tumors; one patient had involvement of the jaw and one had sparse involvement of the peripheral lymph nodes. The antibody titer against Epstein-Barr virus (EBV) capsid antigen was slightly but not significantly elevated in the two patients examined. B-lymphocyte markers were demonstrated in both tumors examined and both showed a weak reaction for intracytoplasmic monoclonal immunoglobulin. The tumor cells from three patients were characterized by chromosome abnormalities. In two patients, the marker chromosome 14q+ was demonstrated; in the third, the investigation was inconclusive because of the absence of one chromosome 14 in all mitoses. This feature of the nonendemic type of BL (in which there is no firm association with EBV) is another trait in common with the endemic type of BL (associated with EBV). (59 refs)

79-6525 A Re-examination of the Alleged Monocytic Features of Hairy-Cell Leukaemia. (Eng) Burns, G. F. (Dept. Haematological Medicine, Univ. Cambridge, Cambridge, England); Cawley, J. C. *Scand J Haematol* 22(5): 386-396; 1979.

Several monocytic features of the hairy cells (HC's) of hairy cell leukemia (HCL) were studied in detail. By means of a rosette assay employing erythrocytes (E's) coated with IgG (EAG), a receptor for the Fc of IgG was shown to be strongly expressed on all HC's, whether in suspension or in monolayer. This receptor was shed and reexpressed over a period of approx 6 hr. In EAG rosette formation, the indicator E's were deformed, and the receptor was not blocked by an antiserum to immune-associated-like antigen. Ultrastructural acid phosphatase cytochemistry showed that HC's phagocytose latex particles, but they do not phagocytose a variety of other particles to a significant extent. These features plus data found in the literature are compatible with the current view that HCL is a form of B-cell lymphoproliferation. (47 refs)

79-6526 Ultrastructural and Immunohistological Study of Immunoblastic Sarcoma Developing in Child with Immunoblastic Lymphadenopathy. (Eng) Morris, J. A. (Dept. Pathology, Univ. Leeds, Leeds LS2 9JT, England); Bird, C. C. *Cancer* 44(1): 171-182; 1979.

The ultrastructural and immunohistological features of the first case of immunoblastic lymphadenopathy progressing to immunoblastic sarcoma to occur in a child (a 7-yr-old boy) is reported. The sarcoma cells showed light and electron microscopic features of transformed lymphocytes (immunoblasts), but it was not possible to establish their B-cell origin using a peroxidase-antiperoxidase technique for the demonstration of intracellular immunoglobulins. In the affected lymph nodes there was marked proliferation of reticulum and endothelial cells, both of which contained numerous intranuclear inclusions that may have been of

viral origin. Ultrastructural studies suggest that the amorphous eosinophilic interstitial material, an important diagnostic morphological feature of immunoblastic lymphadenopathy, results from the oblique sectioning of the elongated and branching cytoplasmic processes of reticulum cells. It is postulated that in immunoblastic lymphadenopathy, the proliferation of reticulum and endothelial cells may be the primary event, perhaps stimulated by viral infection, and that the intense lymphocytic and plasmacytic infiltration and sarcomatous transformation occur as secondary phenomena. (26 refs)

79-6527 The Potential Histogenic Relationship of the Peripheral Nerve to Synovioma. (Eng) Ichinose, H. (Dept. Pathology, Tulane Univ. Sch. Medicine, New Orleans, LA 70112); Powell, L.; Hoerner, H. E.; Derbes, V. J.; Byers, J. F. *Cancer Res* 39(10): 4270-4273; 1979.

Three cases illustrating nerve involvement in synoviomas are reported. A 4.4-cm synovial sarcoma of the endothelioid type was found in the deep fascia of the right upper thigh of a 34-yr-old man with an 18-mo history of severe localized tenderness. The tumor contained typical calcospherites and small nonmyelinated nerves, and the peripheral edges showed myxoid deposits adjoining other nerves. A 2.2-cm synovial sarcoma of the epithelioid type was found infiltrating the fascia of the medial aspect of the left os of the second patient, a 70-yr-old woman. The tumor had interstitial areas of myxoid differentiation and small unmyelinated nerves, and a large neighboring nerve showed prominent atypical proliferation of Schwann cells. In the left axilla of the third patient, a 35-yr-old man with an 18-mo history of pain and numbness in the affected area, a synovial sarcoma with calcospherites, multifocal myxoid areas, and cellular epithelioid areas margined by spindle cell fascicles was found. A large nerve of the brachial plexus passed through the tumor, and several other branches were draped across the exterior surface of the tumor. Nonmyelinated nerves within the interior of the tumor seemed to blend with adjoining cancer spindle cells. The data support the hypothesis that synovioma may be neural in origin. (23 refs)

79-6528 Intrathoracic Meningoceles and Neurofibromatosis. (Eng) Erkulvawatr, S. (Dept. Neurology, Medical Coll. Georgia, Augusta, GA 30901); Gammal, T. E.; Hawkins, J.; Green, J. B.; Srinivasan, G. *Arch Neurol* 36(9): 557-559; 1979.

Four cases of intrathoracic meningoceles associated with neurofibromatosis are reported. In all cases, the diagnosis of neurofibromatosis was antecedent to the discovery of the meningocele. All patients were women (19-60 yr old). One patient suffered from severe paraparesis, two from headaches, and the fourth was seen for evaluation of a possible lung carcinoma following the discovery of a soft-tissue mass on a routine chest roentgenogram. These 4 cases bring to 88 the number of thoracic meningoceles, 75 of which have been associated with neurofibromatosis. Several skeletal abnormalities are associated with this lesion, indicating that osseous dysplasias are intrinsic to the disorder. It is conceivable that a combination of regional vertebral and dural dysplasia could lead to the formation of meningocele. (15 refs)

79-6529 Intracranial Meningiomas Related to External Cranial Irradiation. (Eng) Spallone, A. (Istituto di Neurochirurgia, Universita di Roma, Viale dell'Universita 30, 00185 Rome, Italy); Gagliardi, F. M.; Vagnozzi, R. *Surg Neurol* 12(2): 153-159; 1979.

Two cases of multiple meningiomas following irradiation for tinea capitis and one case of meningioma following radiotherapy for a vascular nevus of the scalp are reported. Two patients (a 51-yr-old man and a 25-yr-old man) had been irradiated in infancy and the third (a 44-yr-old woman) at the age of 5. The patients who had been treated for tinea capitis received <800 R, and the third patient received a total of 1,500 R. The latent period was 25-45 yr, which is much shorter than that usually seen in intracranial meningiomas following high-dose irradiation for intracranial tumors (2-10 yr). The difference in latent period suggests that the oncogenic mechanism is different in the two groups and/or dose-related. The previously reported concept of "misregeneration" may explain the causal relationship between low dose irradiation and the development of meningiomas. This theory could account for the long latency period between irradiation and tumor development and might also explain why the tumor is almost always benign. (39 refs)

- 79-6530 Rhabdomyosarcoma Arising in a Pineal Teratoma. (Eng) Preissig, S. H. (Dept. Pathology, Duke Medical Center, Durham, NC 27710); Smith, M. T.; Huntington, H. W. *Cancer* 44(1): 281-284; 1979.

A rhabdomyosarcoma developed in a pineal teratoma in a 14-yr-old boy and was rapidly fatal despite radiation therapy. The teratoma contained anaplastic spindle cells with cross-striations. This is the second reported case of a pineal teratoma giving rise to a rhabdomyosarcoma. (17 refs)

- 79-6531 Sublingual Keratosis and Malignant Transformation. (Eng) Pogrel, M. A. (H. M. Stanley Hosp., St. Asaph, Wales). *J Oral Pathol* 8(3): 176-178; 1979.

The rate of malignant transformation in 19 patients with sublingual keratosis (SK) was studied. Carcinoma subsequently developed in three patients. The SK patients ranged in age from 48-73 yr and included 12 women and 7 men. Among the patients who developed carcinoma there were two men aged 48 and 61 yr and a 65-yr-old woman. The carcinomas developed 4-7 yr after SK. Eight SK patients were heavy smokers, and carcinoma developed in two of them. A fourth SK patient developed carcinoma of the lateral border of the tongue 5 yr later in an area unaffected by leukoplakia. Of the 16 patients who showed no malignant transformation of leukoplakia, 3 remained unchanged, three had repeated biopsies taken, 4 improved, and 6 could not be evaluated on the basis of available information. In a series of 23 patients with carcinomas of the floor of the mouth, the carcinoma arose in a preexisting white lesion in 8 cases. The results suggest that SK has a considerable risk of malignant transformation and that biopsy and meticulous follow-up are mandatory. (5 refs)

- 79-6532 Herpes Simplex Type 2 Encephalitis Concurrent with Known Cerebral Metastases. (Eng) Manz, H. J. (Dept. Pathology, Georgetown Univ. Medical Center, 3900 Reservoir Rd., Washington, DC 20007); Phillips, T. M.; McCullough, D. C. *Acta Neuropathol (Berl)* 47(43): 237-240; 1979.

The case report of a patient with disseminated Herpes simplex encephalitis concurrent with cerebral metastases from a lung carcinoma is presented. The patient, a 62-yr-old woman developed neurologic deficits 7 mo after pulmonary lobectomy for alveolar cell carcinoma of the lung. Computerized tomography scan of the head demonstrated two metastases with marked peritumoral

edema. Dysphasia and right hand paresis improved with therapy, but she developed rhythmic, involuntary movements of the left hand almost 2 mo later. There was progression to multifocal seizures, grand mal seizures, postictal depression, status epilepticus, and coma; the patient died 9 days after the onset of the movement disorder. At autopsy, bronchoalveolar carcinoma was found to be widely disseminated in the lungs and bones, and three metastases were found in the brain. Bland 'ischemic' necrosis in a pseudolaminar pattern was present in the neocortex. Innumerable Cowdry type A intranuclear inclusion bodies were seen in neurons, astrocytes, and oligodendroglia, and Herpes simplex virus type 2 antigen and Herpes-type virions were identified by immunofluorescence and electron microscopy. This case illustrates the potential for the development of neurologic complications due to more than one mechanism in a patient with systemic cancer. (26 refs)

- 79-6533 Giant Cell Tumor in Paget's Disease of Bone: Familial and Geographic Clustering. (Eng) Jacobs, T. P. (Dept. Medicine, Coll. Physicians and Surgeons, Columbia Univ., 630 W. 168th St., New York, NY 10032); Michelsen, J.; Polay, J. S.; D'Adamo, A. C.; Canfield, R. E. *Cancer* 44(2): 742-747; 1979.

Four patients with benign giant cell tumor and one with probable benign giant cell tumor associated with Paget's disease are reported. Three patients were from one family. All patients claimed ancestors who had emigrated from the same small town in southern Italy, and all were born and raised in northern New Jersey. The cases reported here occurred only in bone affected by Paget's disease. The symptoms were caused by encroachment of the tumor upon neighboring structures, and in no instance did distant metastasis of the primary tumor occur. It is suggested that genetic and possibly environmental factors or a combination of both could be responsible for the linkage of these five patients with this highly unusual neoplasm. (25 refs)

- 79-6534 Cell Surface Proteins and Glycoproteins of Metastatic Murine Melanomas and Sarcomas. (Eng) Nicolson, G. L. (Dept. Developmental and Cell Biology, Univ. California, Irvine, CA 92717). In: *Biological Markers of Neoplasia: Basic and Applied Aspects*. Proceedings of an international conference held 22-26 May 1978, Leesburg, VA. Ruddon, R. W., ed. (New York; Elsevier): 590 pp.; 227-239; 1978.

The cell-surface proteins and glycoproteins of metastatic murine melanomas and sarcomas selected for blood-borne metastatic colonization of specific organs were studied. There were only slight differences in the surface proteins and concanavalin A-binding components of B16 melanoma lines selected for high and low potential for metastasis to the lung. However, surface proteins of approx 95,000 and 100,00 daltons (95K and 100K) were more "exposed" on B16 lines selected for high potential for metastasis to the brain, than on nonselected parental lines. The incorporation of ¹²⁵I into these two components and the ratio of ¹²⁵I-labeled 100K/95K increased with brain selection. Compared with nonselected lines, ovary-selected variant lines of B16 incorporated more ¹²⁵I into surface proteins of approx 155K and 140K. A variant of MSV3T3 sarcoma selected for lung colonization showed greater exposure of two components of 95K and 140K compared with the parental line, and the parental line showed greater exposure of a protein of approx 250K. Affinity chromatographic analysis of the cell-surface glycoproteins of lung-selected and unselected MSV3T3 variants suggested that the 95K component

was bound and eluted and appeared in greater quantity (or exposure) on the lung-selected line, whereas the 250K component was greater (or more exposed) on the parental line. The possible role(s) of the components identified in these studies in the metastatic process remains to be determined. (31 refs)

- 79-6535 Ultrastructure of Chondroid Syringoma. Role of the Myoepithelial Cell in the Development of the Mixed Tumor of the Skin and Soft Tissues. (Eng) Varela-Duran, J. (Dept. Pathology, Univ. Minnesota Hosps., Box 609 Mayo Memorial Building, 420 Delaware St., S. E., Minneapolis, MN 55455); Diaz-Flores, L.; Varela-Nunez, R. *Cancer* 44(1): 148-156; 1979.

The results of an electron microscopic study of a chondroid syringoma that developed in a 61-yr-old man are presented. The tumor nests were formed by clumps, solid cords, and tubular structures distributed diffusely throughout a stroma of varying density. The tumor was comprised of two different types of cells: dark cells forming the inner layer of the tubuloalveolar and ductal structures and having epithelial features and light cells forming the outer layer of the tubular structures and showing myoepithelial differentiation. The myoepithelial cells seemed to be responsible for the production of the chondroid areas and, thus, the mixed appearance of the tumor. The epithelial cells forming the solid tumor nests showed intracytoplasmic luminal formation and other features that favor the origin of chondroid syringomas from the eccrine sweat gland duct. (21 refs)

- 79-6536 Polymorphism of Population of Tumor Cells and Selective Processes. Communication III. Changes in the Ratio of Subpopulations of Ehrlich Ascites Tumor Cells (Strain-ICP) after Exposure to Glucose and Sodium Succinate. (Rus) Fomina, M. M. (Lab. Quantitative Oncology, Inst. Chemical Physics, Moscow, USSR); Minenkova, E. A.; Lankin, V. Z.; Poroshenko, G. G.; Evsejenko, L. S. *Tsitologia* 21(8): 953-958; 1979.

The effect of energy substrates on the polymorphism of a tumor cell population was studied in random-bred albino rats. Animals were given ip transplants of $6-8 \times 10^6$ Ehrlich ascites tumor cells (ICP strain); on days 3-7 after transplantation, mice received ip injections of glucose (100 mg/day) or sodium succinate (10 mg/day). The animals were sacrificed at the end of varying time periods, and the tumor specimens were subjected to cytogenetic analysis. The tumor cell populations from nontreated mice consisted of two subpopulations: one with 44 chromosomes and (A1 + A2 + 2B + C) marker chromosomes, and another with 45 chromosomes and (A + B + 2C) and (A + D + 2C) marker chromosomes. The ip administration of both substrates resulted in a marked shift in the Ehrlich ascites tumor cellularity: there was a marked increase in the frequency of cells carrying 44 chromosomes and the A1 marker (50% on day 5 of transplantation and 100% on day 7) with a corresponding decrease in the frequency of cells with 45 chromosomes and marker A. (10 refs)

- 79-6537 Lung Carcinoma Arising in Bronchopulmonary Sequestration. (Eng) Bell-Thomson, J. (Dept. Thoracic and Cardiovascular Surgery, Maimonides Medical Center, 4802 Tenth Ave., Brooklyn, NY 11219); Missier, P.; Sommers, S. C. *Cancer* 44(1): 334-339; 1979.

A squamous cell carcinoma arising in an area of intralobar bronchopulmonary sequestration in the right lower lobe of a 69-yr-old man is reported. The patient had undergone a bilateral nasal polypectomy and also right maxillary antrostomy for chronic sinusitis at age 63, and developed herpes zoster skin lesions at age 67. He was a heavy cigarette smoker until age 63 and drank 1 pint of whiskey daily. He underwent right posterolateral thoracotomy for the carcinoma and has remained well during the 5 yr since surgery. The presence of intrapulmonary sequestration was indicated by a rounded subpleural portion of lung demarcated peripherally by fibroelastic tissue containing bronchi, bronchiolar cysts, fibrous tissue, and unusually large arteriosclerotic arteries. The squamous cell carcinoma was unusual in showing localized and evidently sluggish invasive growth. Only one other case of cancer in an intralobar sequestration has been reported, and in this case the primary lesion may have been elsewhere and the lesion in the sequestration may have been only a metastasis. (13 refs)

- 79-6538 Cell Surface Sialylation of Glycoproteins and Glycosphingolipids in Cultured Metastatic Variant RNA-Virus Transformed Non-producer BALB/c 3T3 Cell Lines. (Eng) Yogeewaran, G. (Dept. Cancer Biology, Salk Inst. Biological Studies, P.O. Box 1809, San Diego, CA 92112); Sebastian, H.; Stein, B. S. *Int J Cancer* 24(2): 193-202; 1979.

The sialic acid composition and the display of cell-surface sialyl components of several metastatic variant RNA virus-transformed nonproducer BALB/c 3T3 cell lines were studied. The compositions of whole cell total, protein-bound, and lipid-bound sialic acid were not appreciably different. The surface sialic acid was positively correlated with the metastatic properties of the lines. The degree of surface sialylation of neuraminidase-treated and untreated cells revealed that 44%-89% of the exposed galactose and/or N-acetylgalactosamine residues of the total cell-surface saccharides were sialylated in highly and intermediately metastatic lines, but only 11%-30% were sialylated in the poorly metastatic and nonmetastatic lines. The cell-surface glycoproteins and glycosphingolipids contributed equally well in their degree of sialylation, and there was a positive correlation between sialylation in vitro and the metastatic properties of the cells in vivo. The cell-surface proteins labeled by lactoperoxidase-catalyzed iodination showed some minor differences between metastatic variant lines. However, glycoproteins detected by the galactose oxidase labeling of neuraminidase-treated and untreated cells showed major differences in composition between the different lines. Four highly metastatic lines were enriched in several sialylglycoproteins, whereas three nontumorigenic lines and two poorly metastatic or nonmetastatic lines contained unsialylated glycoproteins. The results indicate that there is an enhancement of the degree of sialylation of surface glycoconjugates accompanying metastasis in RNA virus-transformed mouse lines. (48 refs)

- 79-6539 Spontaneous Argyrophil Cell Carcinoid in the Glandular Stomach: Immunohistochemical Study of Gastric Endocrine Cells in Normal and Tumour-bearing Mastomys. (Eng) Hakanson, R. (Farmakologiska Institutionen, Solvegatan 10, S-223 62 Lund, Sweden); Alumets, J.; Sundler, F. *Scand J Gastroenterol [Suppl]* 14(53): 27-32; 1979.

The gastric endocrine cells in normal female mastomys and in mastomys bearing spontaneous argyrophil cell carcinoids of the glandular stomach were studied and compared with those of male Wistar rats and male and female NMRI mice. The number of enterochromaffin-like cells and somatostatin cells in the oxyntic mucosa of normal mastomys was much lower than in the rat and

mouse. Although the number of gastrin cells in antral specimens from mastomys was in the same range as that in the mice and rats, the number of enterochromaffin cells was much higher and the number of somatostatin cells much lower. There was no gastrin or somatostatin immunoreactivity in the argyrophil tumor cells of the mastomys, nor was there any 5-hydroxytryptamine fluorescence. Many tumor cells displayed dopamine fluorescence upon L-dopa pretreatment. The only change apparent in the endocrine cells of the gastric mucosa of tumor bearing mastomys was a reduced number of antral gastrin cells. The reduction seemed to increase with tumor size. A reduction in gastrin cell number was also noted in an animal with a transplanted tumor. (19 refs)

- 79-6540 Clinical, Genetic, and Biostatistical Progress in the Cancer Family Syndrome. (Eng) Lynch, H. T. (Dept. Preventive Medicine, Public Health, Creighton Univ. Sch. Medicine, Omaha, NE 68178); Guirgis, H. A.; Harris, R. E.; Lynch, P. M.; Lynch, J. F.; Elston, R. C.; Go, R. C.; Kaplan, E. *Front Gastrointest Res* 4: 142-150; 1979.

The occurrence of cancer and certain biological markers in members of families prone to carcinoma of the colon and endometrium (ie, cancer family syndrome, CFS) was studied. An approx 50% excess lifetime incidence of colorectal/endometrial cancer among the progeny of matings involving an affected direct-line parent suggested that one-half of the affected progeny received a deleterious cancer-predisposing gene from their heterozygous direct-line parents. Segregation analysis for one pedigree (C-196) supported an autosomal dominant inheritance with gene carriers showing a lifetime susceptibility of 89% and a mean onset at 42.5 yr of age. In pedigree C-120, 15 members distributed over three generations had cancer, including six with cancer of the colon, one with cancer of the stomach, one with cancer of the endometrium, and two with cancer of the ovary. The mean age of onset in this family was 44.5 yr (range, 25-67 yr). In pedigree CFS-196, 19 members were tested for a variety of biological markers, and five of the eight markers studied were utilized in deriving an index score for each individual. The 13 unaffected individuals with affected parents had scores ranging from 2 to 29.8. The scores were significant (mean, 16.1, $p < 0.05$) in 4/13 persons and nonsignificant in the remaining 9 (mean 8.3). (28 refs)

- 79-6541 Neoplastic and Nonneoplastic Lesions in Aging (C57BL/6N x C3H/HeN)_F₁ (B6C3F₁) Mice. (Eng) Ward, J. M. (Tumor Pathology Branch, Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20205); Goodman, D. G.; Squire, R. A.; Chu, K. C.; Linhart, M. S. *J Natl Cancer Inst* 63(3): 849-854; 1979.

Neoplastic and nonneoplastic lesions in 2,543 male and 2,522 female untreated (C57BL/6N x C3H/HeN)_F₁ mice used as controls in carcinogenesis tests were tabulated and evaluated. The most common neoplasms in male mice were hepatocellular adenomas and carcinomas, lymphomas, leukemias, and pulmonary adenomas and carcinomas. In female mice, common tumors included lymphomas, leukemias, pulmonary adenomas and carcinomas, hepatocellular adenomas and carcinomas, and pituitary adenomas. The risk of developing most neoplasms increased with the age of the mouse. Hepatocellular carcinomas metastasized in 12% of animals with these tumors. Other than lymphomas and leukemias, few other tumors metastasized. Non-neoplastic lesions included cystic hyperplasia of the uterus, nephritis, ovarian and uterine cysts, inflammatory lesions of the lung, mineralization in the brain, and focal hyperplasias in several

tissues. The presence of focal hyperplasias in lung and pituitary, adrenal, and thyroid glands suggested early stages of neoplasia. (12 refs)

- 79-6542 Demonstration of α_1 -Antitrypsin in Hepatomas. (Eng) Reintoft, I. (Inst. Forensic Medicine, Odense Univ., DK-5000 Odense, Denmark); Hagerstrand, I. *Arch Pathol Lab Med* 103(10): 495-498; 1979.

Sixty-nine primary malignant hepatomas were examined for the presence of α_1 -antitrypsin (α_1 -AT) in tumor cells using immunohistochemical methods. Twenty-eight tumors were α_1 -AT-positive. Diastase-resistant, PAS-positive, and α_1 -AT-positive globules were seen in 11 hepatocellular tumors and 1 cholangiocellular tumor, thus simulating the pattern of α_1 -AT accumulation in hepatocytes in subjects carrying the Z-gene for α_1 -AT. In fact, this pattern was seen in normal liver tissue in eight cases of hepatocellular carcinoma. In ten hepatocellular tumors, the reaction was finely granular throughout the hepatocytic cytoplasm, but was present in only a small number of cells. Still fewer cells were positive in six cholangiocarcinomas. The globular α_1 -AT in tumor cells may be genetically determined when associated with the Z-gene. Reappearance of fetal gene products may have occurred in three hepatocarcinomas that showed globules positive for α -fetoprotein as well as for α_1 -AT. (12 refs)

- 79-6543 Detection of Hepatitis B Surface Antigen in Fixed Tissues of Patients with Cirrhosis and Hepatoma. (Eng) Theodoropoulos, G. (2 Dryadon St., Chalandri-Attikis, Greece); Nakopoulou, L.; Repanti, M.; Papacharalampous, N.; Melissinos, K. *Virchows Arch [Pathol Anat]* 382(3): 293-300; 1979.

Light microscopy was used to detect hepatitis B surface antigen (HBsAg) in liver specimens from 79 patients with cirrhosis and 99 with hepatoma. The study was carried out on fixed material using orcein staining, immunoperoxidase staining, and indirect immunofluorescence (IIF). HBsAg was detected by radioimmunoassay in the serum of 38 patients with cirrhosis and 36 with hepatoma. HBsAg-positive cells were observed in 31 of the former by orcein staining and in 32 by the immunoperoxidase and IIF methods. Among the 36 seropositive hepatoma patients, HBsAg was detected in the surrounding nonneoplastic part of the liver, cirrhotic or not, in 30 by orcein staining and in 34 by the immunoperoxidase and IIF methods. Positive solitary tumor cells were seen occasionally in 16/36 patients using orcein, in 9/36 using peroxidase, and in 7/36 by IIF. The results do not support the hypothesis of a direct oncogenic effect of HBsAg on liver cells, since this antigen was detected mainly in the nonneoplastic part of the liver tissue and only occasionally in the tumor cells. Of the 63 seronegative hepatoma patients, 3 showed some round, orcein-positive inclusion bodies in the cytoplasm of neoplastic and non-neoplastic cells; these bodies were not stained by the two immunological methods. (23 refs)

- 79-6544 Spontaneous Tumors and Common Diseases in Three Types of Hamsters. (Eng) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42d St. and Dewey Ave., Omaha, NE 68105); Althoff, J.; Salmasi, S. Z.; Stepan, K. *J Natl Cancer Inst* 63(3): 797-811; 1979.

Three types of hamsters designated as inbred cream (Epp/e/e), linebred white (EPP/c^dc^d/RB/A), and linebred albino (EPP/c^dc^de/e) were examined histopathologically for spontaneous

disease. All hamsters were maintained simultaneously for life under identical standard laboratory conditions. Survival time in cream hamsters (CH) was shorter than that in white hamsters (WH) and that in albino hamsters (AH). More tumors and malignant lesions unrelated to survival were found in AH compared with CH and WH; in addition, the multiplicity of neoplasms was more pronounced in AH. The predominating tumor types differed in each line: Pancreatic islet cell neoplasms were most common in CH; adrenal gland tumors predominated in WH; and thyroid gland tumors were more frequent in AH. The relative incidence of spontaneous tumors varied among the lines. Some tumors seemed strain-specific and were not seen in other lines; eg, malignant melanomas occurred only in CH and WH. Certain neoplasms, eg, those of the thyroid and adrenal gland were found more often in one sex than the other. The three hamster groups differed also in nonneoplastic disease. Detailed histopathologic findings are presented and compared with data on the Syrian golden hamster, the ancestral line of these three groups. (28 refs)

- 79-6545 **Metanephrogenic Epithelial Hamartomas. A Contribution to their Morphology, Evolution, and Significance.** (Ger) Stambolis, C. (Institut Pathologie, Universitätsklinikum der Gesamthochschule Essen, Hufelandstrasse 55, D-4300 Essen, W. Germany). *Zentralbl Allg Pathol* 123(1/2): 62-70; 1979.

Neoplastic metanephrogenic lesions without mitoses or signs of malignancy were found in the intact renal parenchyma of three patients (1 boy, 2 girls, aged 3.5, 4, and 5 yr, respectively) with Wilms' tumor. These lesions represented regressive forms of the nodular renal blastema-nephroblastomatosis complex. They were characterized as simple or diffuse metanephrogenic epithelial hamartomas. Small lesions showed involution resulting in scars. In the central parts of larger lesions, cysts and adenomas were detected. The adenomas were multicentric and revealed compact-epithelial, papillary-psammomatous, cystic-multilocular, and tubulopapillary forms. All lesions were subcapsular and occasionally occurred in the zone of the columnae renales. There appears to be a close relationship between the metanephrogenic epithelial hamartomas and the nodular renal blastema-nephroblastomatosis complex; they can occur in the same kidney, and often also bilaterally. They are most frequent in patients with Wilms' tumors. (26 refs)

- 79-6546 **On the Nature and Significance of Nodular Renal Blastema.** (Ger) Stambolis, C. (Institut Pathologie, Universitätsklinikum der Gesamthochschule Essen, Hufelandstrasse 55, D-4300 Essen, W. Germany). *Zentralbl Allg Pathol* 123(1/2): 3-8; 1979.

Neoplastic lesions found in intact renal parenchyma of 24 children with Wilms' tumors (12 boys, 12 girls; average 31 mo) are presented. The patients included two brothers, aged 3 and 4 yr, and a girl with aniridia. Nodular renal blastema and multiple small Wilms' tumors were found in one patient, a 6-mo-old boy with hemiatrophy. Metanephrogenic hamartomas were found in three other patients. Nodular renal blastema, small Wilms' tumors, and metanephrogenic hamartomas occur alone, are mostly bilateral, and usually occur in younger children. In older children, these neoplastic lesions are almost always associated with Wilms' tumor. They are related to certain congenital anomalies. The findings suggest that there is a genetic relationship between the nodular renal blastema-nephroblastomatosis complex and Wilms' tumor. (31 refs)

- 79-6547 **Deficiency of Dopamine- β -hydroxylase. A New Mechanism for Normotensive Pheochromocytomas.** (Eng) Feldman, J. M. (Duke Univ. Medical Center, Box 2963, Durham, NC 27710); Blalock, J. A.; Zern, R. T.; Shelburne, J. D.; Gaede, J. T.; Farrell, R. E.; Wells, S. A. *Am J Clin Pathol* 72(2): 175-185; 1979.

The case of a 28-yr-old normotensive man with bilateral pheochromocytomas (PCCs) is compared with those of four hypertensive patients with PCCs. The tumors of the normotensive patient contained large amounts of dopamine (DA), small quantities of norepinephrine (NE), and no epinephrine (E). The PCCs of the hypertensive patients contained large amounts of DA, NE, and, in some tumors, E. The small amount of NE in the tumors of the normotensive patient was due to a dopamine- β -hydroxylase deficiency in the tumors. The small amount of E was due to a deficiency in phenylethanolamine-N-methyltransferase (PNM), as well as to deficiency in the PNM substrate, NE. Many of the electron-dense secretory granules in the predominantly DA-containing PCCs of the normotensive patient were morphologically similar to granules of NE. However, these granules tended to be slightly smaller and more variable in size and shape than the NE-containing granules of one hypertensive patient. The large amount of homovanillic acid (HVA) in the preoperative, but not the postoperative, urine of the normotensive patient suggested that the tumors secreted DA, whereas the normal excretion of HVA by the hypertensive patients suggested that their tumors did not secrete DA. The absence of hypertension in a patient with PCC might be due to a deficiency in tumor dopamine- β -hydroxylase activity, with a resulting increase in DA secretion and decrease in NE secretion. (40 refs)

- 79-6548 **The Prognostic Value of Axillary Lymph Gland Sinus Histiocytosis in Female Mammary Carcinoma.** (Eng) Yu, H. (Dept. Pathology, Cancer Inst., Chinese Acad. Medical Sciences, Republic of China). *Chin Med J* 92(5): 353-359; 1979.

The relationship between the axillary lymph node sinus histiocytosis (SH) reaction and the prognosis of breast cancer was studied using 228 breast biopsy specimens from untreated female breast cancer patients and 7,586 lymph nodes. The 5- and 10-yr survival rates among the 228 patients were 58.8% and 46.9%, respectively. The SH reaction was mild (SH+) in 35 cases, moderate (SH++) in 92 cases, and marked (SH+++) in 101 cases. The 5-yr survival rate was 22.9%, 45.7%, and 83.2% among those with SH+, SH++, and SH+++ reactions, respectively ($p < 0.002$). Prognosis was influenced by the presence and extent of lymph node metastasis, but the good prognosis associated with increased SH reaction was demonstrated even in patients with lymph node metastases. The relationship between intensity of the SH reaction and survival rate was most obvious in clinical Stages II and III and in pathologic typing groups II₁, II₂, and III. This indicates the importance of the body's reticuloendothelial system immunity reaction in fighting tumors. (7 refs)

- 79-6549 **Paracortical Activity in the Lymph Nodes Draining Female Breast Carcinoma.** (Eng) Syrjanen, K. J. (Dept. Pathology, Jorvi Hosp., 02740 Espoo 74, Finland). *Neoplasma* 26(1): 95-102; 1979.

A series of 302 consecutive breast carcinomas seen at a Finnish hospital between 1960 and 1976 were assessed histologically, with special attention being focused on the nuclear grade of the tumor, the stromal lymphocyte reaction, and the morphology of the paracortical areas of the regional lymph nodes. These morphologic

parameters were correlated with the 5-yr survival data of the patients. The nuclear grade of the primary tumor was directly related to 5-yr survival, as was the paracortical activity of the regional lymph nodes. The paracortical activity was inversely related to the frequency of nodal metastases, which were a sign of poor prognosis. The morphology of the regional lymph node paracortex is valuable in evaluating host resistance criteria in association with breast carcinoma. (19 refs)

- 79-6550 Malignancies Associated with Hemorrhagic Gastritis. (Eng) Chait, M. M. (Dept. Medicine, Gastroenterology Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Winawer, S. J. *Am J Proctol Gastroenterol Colon Rect Surg* 30(4): 14-16; 1979.

The possibility of an association between specific malignant states and hemorrhagic gastritis was evaluated in 82 cancer patients with hemorrhagic gastritis diagnosed during a 5-yr period. Fifty-six patients were under severe physiological stress; 26 were without such stress but were receiving exogenous gastric irritants (salicylates, alcohol, indomethacin, corticosteroids). The greatest proportion (18/56) of patients in the stressed group had a hematologic malignancy; in the general hospital population during the study period, this accounted for only 9% of all cancers. In the nonstressed group, the most common malignancy was breast cancer (11/26), but its distribution was similar in the nonstressed patients and in the general cancer population (22%). Twenty-five nonstressed patients were receiving salicylates. A malignancy occurred in the stomach of four stressed patients and two nonstressed patients. A history of peptic ulcer disease was documented in eight stressed and seven nonstressed patients. Chemotherapeutic agents such as 5-fluorouracil, cyclophosphamide, and bleomycin were administered to 12 stressed patients and 4 nonstressed patients. These findings indicate that patients with hematologic malignancies are susceptible to stress ulcer bleeding and that chemotherapeutic agents, corticosteroids, and a history of peptic ulcer disease may be potentiating factors in the development of hemorrhagic gastritis in cancer patients. (17 refs)

- 79-6551 Menopausal Genital Tract Hemorrhages. A Report of 143 Cases. (Fre) Lieveaux, A. (Service de Gynecologie, Hopital Lariboisiere, 2 rue Ambroise-Pare, 75010 Paris, France). *Gynecologie* 30(3): 211-215; 1979.

The causes of genital tract hemorrhage were analyzed in 143 menopausal women. Cancer was identified as the cause of the hemorrhage in 12/143 women: there were 9 endometrial adenocarcinomas, including 1 intraepithelial adenocarcinoma; 2 epitheliomas of the uterine cervix; and 1 epithelioma of the Fallopian tube. Eleven of the patients were 57-67 yr old, and the twelfth was 81 yr old. Endocervical polyps were found in 12/143 women, benign endometrial polyps in 5, fibrous intracavitary polyps in 4, and estrogen-secreting tumors in 2. The findings indicate that, contrary to an earlier belief, cancer is a rather rare cause of genital tract hemorrhage in menopausal women. (20 refs)

- 79-6552 Endometrial Carcinoma in Previously Ovariectomized Patients. (Eng) Gal, D. (Dept. Obstetrics and Gynecology, Brookdale Hosp. Medical Center, Brooklyn, NY 11212); Neuhoff, S.; Tancer, M. L. *Gynecol Oncol* 8(1): 44-48; 1979.

Three cases of endometrial adenocarcinoma (EAC) occurring in women who had previously undergone bilateral oophorectomy (BO) and who had not used postmenopausal estrogens are reported. A 63-yr-old nulligravida who had undergone BO for ovarian cysts at age 33 was diagnosed as having EAC Stage IA, Grade I. A 73-yr-old nulligravida who had undergone BO 40 yr previously was diagnosed as having well-differentiated EAC Stage IB, Grade I. A 72-yr-old nulligravida who had undergone BO 37 yr previously was diagnosed as having well-differentiated EAC Stage IA, Grade I. The adenocarcinoma had invaded the myometrium to a depth of one-third its thickness. Endocrine studies indicated low preoperative levels of endogenous androgens without significant postoperative (hysterectomy) variation. Luteinizing hormone and follicle-stimulating hormone levels decreased after hysterectomy. These results are consistent with the possibility of a relationship between the uterus and pituitary activity in patients with endometrial cancer. (30 refs)

- 79-6553 Early (Stage A) Prostatic Cancer. IV. Methodological Criteria for Histopathological Diagnosis. (Eng) Battaglia, S. (Istituto di Anatomia e Istologia Patologica, Università di Modena, Via Berengario 4, I-41100 Modena, Italy); Barbolini, G.; Botticelli, A. R. *Virchows Arch [Pathol Anat]* 382(3): 245-259; 1979.

The incidence, morphology, and etiology of Stage A prostatic cancer or prostatic microcarcinoma (PMC) were studied. The prostates of 100 patients treated by subtotal prostatectomy for benign prostatic hyperplasia (BPH) were analyzed by routine and step-section techniques. The incidence of PMC was 41% by the former and 86% by the latter technique. Assessment of the size of PMC, as measured by the sum of the two main diameters, resulted in three PMC groups: A₁, A₂, A₃. The last of these may represent a frankly malignant condition, judged by size and histological appearance. The number of multicentric foci increased from A₁ to A₃. Histologically, A₁ and A₂ consisted of clear-celled tubular adenocarcinomas, but A₃ showed a variable histological pattern (7 clear-celled tubular adenocarcinomas, 4 cribriform adenocarcinomas, and 1 dark-celled tubular adenocarcinoma). A₁ decreased and A₂ and A₃ increased with age. (132 refs)

See also:

- *(Rev.): 79-6004, 79-6035, 79-6068, 79-6087, 79-6088, 79-6089, 79-6090, 79-6091, 79-6092, 79-6093, 79-6094, 79-6095, 79-6096, 79-6100, 79-6118, 79-6123.
 *(Chem.): 79-6129, 79-6132, 79-6133, 79-6135, 79-6136, 79-6138, 79-6140, 79-6143, 79-6145, 79-6152, 79-6161, 79-6171, 79-6175, 79-6201, 79-6202, 79-6205, 79-6215, 79-6222, 79-6224, 79-6225, 79-6226, 79-6233, 79-6238, 79-6255, 79-6256, 79-6259, 79-6260, 79-6271, 79-6273, 79-6275, 79-6276, 79-6318, 79-6319, 79-6341, 79-6342, 79-6347, 79-6348, 79-6349.
 *(Phys.): 79-6353, 79-6359, 79-6361, 79-6362, 79-6367, 79-6368, 79-6369, 79-6370, 79-6376, 79-6378.
 *(Viral): 79-6422.
 *(Immun.): 79-6471, 79-6473, 79-6484, 79-6485, 79-6487, 79-6493, 79-6512, 79-6517.
 *(Epid.-Biom.): 79-6554, 79-6561, 79-6563, 79-6572, 79-6582.

EPIDEMIOLOGY AND BIOMETRY

- 79-6554 Tumors of the Eye and Adnexa in the Sudan. (Eng) Malik, M. O. (Pathology Dept., Faculty of Medicine, P.O. Box 2925, Riyadh, Saudi Arabia); El Sheikh, E. H. *Cancer* 44(1): 293-303; 1979.

The frequency, sex and age distribution, site, pathologic types, and geographic and racial distribution of 854 tumors of the eye and adnexa in Sudanese patients were analyzed. Of 279 primary malignant tumors (frequency ratio 4.3%), conjunctival squamous carcinoma was the commonest (50.4%), followed by retinoblastoma (20.8%) basal cell carcinoma (6.1%), and malignant melanoma (4.6%). Conjunctival carcinoma and allied epithelial lesions occurred much more often in Northern than in Southern Sudan, and no basal cell carcinoma of the eyelids was recorded in the latter. Retinoblastoma and melanoma showed certain tribal predilections. Most cases of Burkitt's lymphoma occurred in Southern Sudan. It is concluded that geographic and racial factors play important roles in determining the frequency and pattern of eye neoplasms in the Sudan. (60 refs)

- 79-6555 Lipoma of the Cauda Equina (Lumbosacral Lipoma): A Study of 74 Cases Operated in Childhood. (Eng) Rickwood, A. M. (Children's Hosp., Sheffield S10 2TH, England); Hemalatha, V.; Zachary, R. B. *Z Kinderchir Grenz* 27(2): 159-169; 1979.

In a series of 74 cases of lipoma of the cauda equina operated in childhood, females outnumbered males by 2 to 1, and associated congenital anomalies were uncommon. Obvious paralysis was rarely present at birth, but it became progressively more common with age. In most patients, the neurological status remained unchanged postoperatively. Long-term follow-up revealed that there was a high incidence of neurogenic bladder dysfunction and lower limb paralysis in these patients. Early operative intervention reduced the more severe degrees of leg paralysis, but had relatively little impact on the incidence of minor leg paralysis and neurogenic bladder. (15 refs)

- 79-6556 Racial Differences in Melanoma Incidence. (Eng) Crombie, I. K. (Birmingham Regional Cancer Registry, Queen Elizabeth Hosp., Birmingham, England). *Br J Cancer* 40(2): 185-193; 1979.

The incidences of malignant melanoma recorded by 59 population-based cancer registries distributed throughout the world were investigated to determine the effects on these incidences of race and skin color. White populations exhibited a wide range of melanoma incidence, and women commonly, although not invariably, had a higher incidence than men. Nonwhite populations experienced in general a much lower incidence of melanoma, although there was some overlap of white and nonwhite rates. No predominant sex difference emerged among nonwhites. Populations of African descent had a higher incidence than those of Asiatic origin, but it was concluded that this was due largely to the high frequency of tumors among Africans on the sole of the foot. A clear negative correlation between degree of skin pigmentation and melanoma incidence emerged for the exposed body sites. These data provide strong support for the hypotheses that UV radiation is a major cause of malignant melanoma and that melanin pigmentation pro-

tections against it. Further research is required to elucidate the etiology of melanoma of the sole of the foot. (31 refs)

- 79-6557 Cancer Mortality in 1970-1972 Among Polish-Born Migrants to England and Wales. (Eng) Adelstein, A. M. (Office Population Censuses and Surveys, Medical Statistics Div., St. Catherine's House, 10 Kingsway, London WC2B 6JP, England); Staszewski, J.; Muir, C. S. *Br J Cancer* 40(3): 464-475; 1979.

The cancer mortality of Polish migrants to England and Wales during 1970-1972 was compared with that prevailing in England and Wales and that prevailing in Poland; these data were compared with previously published data for Polish-born migrants in the US and in Australia. Compared with mortality rates in both their country of birth and immigration, Polish migrants had intermediate values for cancers of the stomach, intestinal tract, and lung. For age-groups >74 yr, lung cancer mortality among the migrants was higher than that in Poland or that in England and Wales. Polish migrants had a higher mortality from lymphomas in both sexes and from leukemia and esophageal cancer in men than in Poland or in England and Wales. Female breast cancer mortality among Polish migrants was much higher than in Poland, approaching the high mortality rates prevailing in England and Wales. A similar trend was observed for prostate cancer, but comparisons were based on smaller numbers and on less reliable data. Follow-up of these migrants might help elucidate the relative roles of environment and length of residence in differences in cancer risk among these populations. (9 refs)

- 79-6558 Cancers of the Large Bowel. Associated Disorders in Individuals. (Eng) Adelstein, P. (Unit Clinical Epidemiology, Oxford Regional Health Authority, Old Road, Headington, Oxford, England); Baldwin, J. A.; Fedrich, J. *Cancer* 43(6): 2553-2557; 1979.

Data collected in the 1963-1967 Oxford Record Linkage Study were analyzed to ascertain any previously unsuspected associations between cancer of the large bowel and other diseases in individuals and to quantify the relative risks of disorders already known to be associated. In men, significant associations were shown between cancer of the large bowel and cancer of the prostate. In women, cancer of the colon was associated with breast cancer, and cancer of the rectum was associated with a mixed group of genital cancers. The relative risk of colorectal cancer associated with previous benign neoplasms of the large bowel and with ulcerative colitis was 20 and 25, respectively. There was no significant association with appendicitis or longstanding diverticular disease. (8 refs)

- 79-6559 Dietary Fibre and Regional Large-Bowel Cancer Mortality in Britain. (Eng) Bingham, S. (Dunn Clinical Nutrition Centre, Addenbrooke's Hosp., Cambridge, England); Williams, D. R.; Cole, T. J.; James, W. P. *Br J Cancer* 40(3): 456-463; 1979.

The relationship between food intake and large bowel cancer was assessed by calculating the av intakes of foods, nutrients, and

dietary fiber in the different regions of Great Britain and relating these to the regional pattern of death from colon and rectal cancers between 1969 and 1973. No significant associations were found with the consumption of fat, animal protein, or beer, nor with current estimates of total dietary fiber intake. Av intakes of the pentose fraction of total dietary fiber, as well as of vegetables other than potatoes, were negatively correlated with the truncated age- and sex-standardized death rates from colon cancer ($r = -0.960$ and -0.940). Specific components of dietary fiber may therefore inhibit colon carcinogenesis. (28 refs)

- 79-6560 Alcohol and Oesophageal Cancer: An Assessment of the Evidence from Routinely Collected Data.** (Eng) Chilvers, C. (Epidemiological Monitoring Unit, London Sch. Hygiene and Tropical Medicine, London, England); Fraser, P.; Beral, V. *J Epidemiol Commun Health* 33(2): 127-133; 1979.

Mortality and morbidity due to esophageal cancer in England and Wales were investigated. The mortality rate declined after 1911, then increased during the 1950's in all except the oldest age groups. The generation of males born in 1906 had a lower mortality than any preceding or succeeding generation. Morbidity rates increased 52% among males and 54% among females during the period 1962-63 to 1973-74. Since 1900, there was a steady decline in the consumption of alcohol until after World War II, when consumption increased. Consumption of beer contributed to total alcohol consumption. For both males and females, cohort mortality was closely correlated with the per capita consumption of total alcohol when the cohort was aged 25-29 yr ($p < 0.01$). Cigarette smoking has increased steadily since 1905 except for a sharp decline between 1946 and 1950. There was no relationship between cigarette consumption in different generations and mortality from esophageal cancer. Mortality from cirrhosis of the liver and esophageal cancer was highly correlated on a regional basis among males ($p < 0.1$) but not among females. Internationally, for males, but not females, there was also an association between total alcohol consumption and esophageal cancer ($p < 0.01$); there was a weaker association with wine ($p < 0.05$) but not beer or spirit consumption. The international data suggest that ethyl alcohol itself rather than any specific alcoholic beverage is associated with esophageal cancer. (29 refs)

- 79-6561 The Incidence of Gastric Cancer and High-Risk Groups.** (Pol) Rybicka, J. (Klinika Gastroenterologii, Instytut Chorob Wewnętrznych Śląskiej Akademii Medycznej, ul. Medyków, 40-752 Katowice, Poland); Gibinski, K.; Nowak, A.; Czarnecka, K. *Pol Arch Med Wewn* 61(5): 403-410; 1979.

A prospective study was made of 4,538 patients who had undergone diagnostic endoscopy of the upper digestive tract. Three gastric cancer risk groups were identified: Group A (181 patients who underwent partial gastric resection), Group B (754 patients with a family history of cancer), and Group C (155 patients with anacidity). The overall gastric cancer incidence was 194/4,538; the group incidence was 12/181 in Group A, 31/754 in Group B, 14/155 in Group C, and 137/3,448 in the remaining patients. The incidence of endoscopic changes (inflammation, erosion, ulcers, and deformation of the pylorus and duodenal bulb; inflammation, erosion, ulcers and polyps of the stomach) did not differ substantially between the three high-risk groups. The mean age of the tumor-free patients was 48.3 yr in Group A, 47 yr in Group B, and 47.4 yr in Group C. The mean age of the gastric cancer patients was: 58.6 yr in Group A, 57.8 yr in Group B, and 67.2 yr in Group C. In Group A, the postresection incidence of gastric cancer was 4/90 after 5-9 yr, 0/50 after 10-14 yr, 1/19 after

15-19 yr, 2/12 after 20-24 yr, 2/5 after 25-29 yr, and 3/5 after 30-34 yr. The findings indicate that patients with past gastric resection, a family history of cancer, and anacidity should be subjected to endoscopic examinations at regular intervals to increase the detection of early gastric cancer. (19 refs)

- 79-6562 Ewing's Sarcoma: An Approach to Radiological Diagnosis.** (Eng) Lombardi, F. (Istituto Nazionale Tumori, Via G. Venezian, 1, 20133 Milan, Italy); Gasparini, M.; Gianni, C.; Petrillo, R.; Tesoro-Tess, J. D.; Volterrani, F.; Musumeci, R. *Tumori* 65(3): 389-399; 1979.

The radiographs of 83 patients with histologically confirmed Ewing's sarcoma were studied. Of the 49 male and 34 female patients, 59% were less than 15 yr of age. Pain was present in 79% and local swelling in 55%, and in two children, the pain was associated with paraplegia. The av time from onset of symptoms to diagnosis was 20 wk. The most common site of involvement was the long (54%) and flat (35%) bones; the small bones were involved in 8%, and the onset was extraosseous in 3%. The diaphysis alone was the site of disease in 41% of the patients, the metaphysis alone in 5%, and both regions were simultaneously involved in 54%. The radiographic findings were always clearly positive. The incidence of chest metastases was 24%, and bone metastases were found in 17/78 patients (22%). The incidence of lymph node metastases in 40 patients without widespread disease was 13%. Two patients had metastatic soft tissue masses. Fifty-seven patients were considered to have localized and 26 widespread disease. In the patients with initially localized disease, metastases later appeared in 28/57 (49%). (20 refs)

- 79-6563 Oesophageal Lesions in Northern Iran: A Premalignant Condition?** (Eng) Crespi, M. (Regina Elena Inst., Rome, Italy); Grassi, A.; Amiri, G.; Munoz, N.; Aramesh, B.; Mojtabai, A.; Casale, V. *Lancet* 2(8136): 217-220; 1979.

To identify possible precancerous lesions of the esophagus, 218 men and 212 women (15-70 yr old) in northern Iran were examined endoscopically. Of the 430 subjects, 43% were of low and 43% were of medium socioeconomic status. Unspecific gastrointestinal symptoms of long duration were present in 39%, the dental condition was poor in 69%, esophagitis was found in 86%, and esophageal varices were observed in 14%. Esophageal cancer was diagnosed endoscopically in seven patients. Biopsies of 418 patients showed chronic esophagitis in 80%, and acanthosis accompanied by slight hyperkeratosis and parakeratosis was present in a few. Invasive carcinoma was detected in 11 subjects. In general, there was good correlation between the endoscopic and histological findings. Esophagitis involved the middle and lower thirds of the esophagus (the common sites for esophageal cancer) in 90% of affected patients. A family history of esophageal cancer was found in 28% of the subjects with normal esophaguses, 30% of those with esophagitis, and 4/11 patients with cancer. The very high prevalence of chronic esophagitis in northern Iran, where a high incidence of esophageal cancer has also been reported, suggests that these two lesions are associated. (18 refs)

- 79-6564 Correlation Between Cancer Mortality and Alcoholic Beverage in Japan.** (Eng) Kono, S. (Dept. Public Health, Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan); Ikeda, M. *Br J Cancer* 40(3): 449-455; 1979.

Geographical correlations between standardized cancer mortality ratios (SMRs) and consumption of different types of alcoholic

beverages (sake, synthetic sake, shochu, beer, wine, and whiskey), cigarette smoking, and urbanization were examined for all 46 prefectures in Japan. Suggestive correlations were observed between esophageal cancer in males and both shochu and whiskey drinking ($r = 0.27$ and 0.22 respectively), between rectal cancer in males and wine consumption ($r = 0.45$), and between cancer of the prostate and shochu drinking ($r = 0.50$). These correlations were also confirmed by the partial correlations between cancer SMRs and consumption of alcoholic beverages in general when urbanization and cigarette smoking variables were controlled. Although cancer of other sites also correlated with certain types of alcoholic beverages, these associations seemed to be secondary to other factors. The validity of higher-order partial correlations and the problems of correlation study are discussed. (23 refs)

- 79-6565 Role of Diet, Alcohol and Tobacco in Oesophageal Cancer, as Illustrated by Two Contrasting High-Incidence Areas in the North of Iran and West of France. (Eng) Tuyns, A. J. (International Agency Res. Cancer, 150 Cours Albert Thomas, F-69372 Lyon Cedex 2, France); Pequignot, G.; Jensen, D. M. *Front Gastrointest Res* 4: 101-110; 1979.

The role of diet, alcohol, and tobacco in the etiology of esophageal cancer (EC) was studied based on data from high-incidence areas in northern Iran and western France. In northern Iran, overall diet in the high-incidence regions was poorer than in other regions, and the consumption of tea by males was much greater. Opium use was also widespread in the high-incidence areas. In western France, pyridoxine and daily alcohol intake by EC patients was approx two-fold greater than by controls, and the total caloric intake by the EC patients was higher. The EC patients ate less meat; more offals; more salted butter; less fatty foods other than butter and oil; more vegetables, potatoes, and smoked fish; and less chocolate than the controls. There were fewer consumers of mineral water and more consumers of beer, cider, wine, and cider distillates among the EC cases than among the controls. The data do not indicate the existence of one common carcinogen present in the diet which might be considered the sole agent of EC. (26 refs)

- 79-6566 Carcinoma of the Oesophagus in Indian Jews in Beersheba, Israel. (Eng) Odes, H. S. (Gastroenterology Unit, Soroka Univ. Hosp., Beersheba, Israel); Krawiec, J. *Front Gastrointest Res* 4: 96-100; 1979.

The incidence of esophageal carcinoma (EC) in Beersheba, Israel during the period 1961-1977 was studied. Of the 21 cases of EC recorded, 9 were among Jews of Indian origin and 12 were among Iraqi, Moroccan, Iranian, and Ethiopian Jews (Sephardi Jews) and European Jews (Ashkenazi Jews). The Indian group included 3 men and 6 women, all of whom presented with dysphagia of less than 3 mo duration and tumors in the middle or lower third of the esophagus. Eight patients had squamous carcinomas, and one had an anaplastic tumor. The non-Indian group included eight men and four women. The middle esophagus was involved most often among the Ashkenazi Jews, and the lower esophagus was the usual site in the Sephardi group. Squamous tumors were present in 10 patients, and 1 patient had an anaplastic carcinoma in the upper esophagus. All patients had dysphagia of recent onset. Indian Jews presented at a mean age of 53.5 yr and non-Indian Jews at 65.5 yr ($p < 0.01$); there were not significant age differences among Ashkenazi and Sephardi Jews. The Indian and non-Indian patients did not differ significantly with respect to average period of residence in southern Israel. (8 refs)

- 79-6567 Some Epidemiological Aspects of Postmenopausal Bleeding and Endometrial Carcinoma in Israeli Women of Different Ethnic Groups. (Eng) Schachter, A. (Dept. Obstetrics and Gynecology, Beilinson Medical Center, Tel Aviv Univ. Medical Sch., Tel Aviv, Israel); Segal, A.; Bahary, C.; Joel-Cohen, S. J. *Cancer Cytol* 19(1): 13-20; 1979.

Epidemiologic aspects of postmenopausal bleeding (PMB) and endometrial carcinoma (EC) were studied in 856 Israel residents with PMB (537 Western origin, 208 Eastern, 111 Israeli), 123 with EC (82 Western, 21 Eastern, 20 Israeli), and 996 controls. The av ages were 56 yr and 58.4 yr for the PMB and EC patients, respectively. Menarche began before the age of 13 yr in 83.5% of the EC patients, 66.4% of the PMB patients, and 48.2% of the controls. The av ages at menopause were 48.6, 51.8, and 49.5 yr for the PMB, EC, and controls, respectively. Of the PMB patients, 3.2% were single, compared with 4.1% of the EC group. Thirteen percent of the EC patients were childless, compared with 6.3% of the controls. The av length of sexual life was 34.3 yr for the EC women, 31.4 yr for the PMB women, and 29.5 yr for the controls. An additional primary malignancy was noted in 18.7% of EC cases, 6.1% of PMB cases, and 6.6% of controls. The EC and PMB patients did not differ significantly with respect to previous estrogen therapy. Diabetes was observed in 9.8% of EC patients, 6.3% of PMB patients, and 3.8% of controls. The incidence of obesity was 33.8% in the EC group compared with 17.3% in the control group. The incidence of hypertension in EC patients (36.6%) was double that of the controls, and estrogenic activity in these women was greater than expected for women of their age. Fibroids were present in 15.4% of the EC patients, 8.2% of the PMB patients, and 6.68% of the controls. (31 refs)

- 79-6568 Risk Factors in Endometrial Carcinoma with Special Reference to the Use of Estrogens. (Eng) Salmi, T. (Dept. Obstetrics and Gynecology, Univ. Turku, Turku, Finland). *Acta Obstet Gynecol Scand [Suppl]* 86: 119 pp.; 1979.

A literature review concerning endometrial cancer epidemiology and estrogen use as a risk factor in endometrial carcinoma is presented together with an original case-control study. The study included personal interviews and was conducted to determine the possible risk factors of endometrial carcinoma with emphasis on the role of exogenous hormones. The cases were 318 endometrial carcinoma patients treated during 1970-1976 in Finland. Controls were matched for age within 5 yr, wt, and social class to form 282 matched pairs. The mean wt of the endometrial carcinoma patients was 73.3 kg, and that of the controls was 66.4 kg. Of the 318 patients, 26.1% were considered obese, compared with 11.8% of the controls. Analysis of the use of continuous medication (hormones excluded) indicated that the relative risk of endometrial carcinoma was 2.4 among those using medication for diabetes mellitus and 1.9 among those using digitalis. Controls had used hormones for some gynecological indication significantly ($p < 0.05$) more often than did the patients, but patients had received hormones because of menstrual disorders significantly more often than did controls. The duration and scheme of estrogen treatment did not differ between patients and controls. It is concluded that obesity may be the main risk factor in endometrial carcinoma. A long-standing endogenous hormonal imbalance manifesting itself as a menstrual disorder and leading to hormone therapy may increase endometrial carcinoma risk. The use of exogenous estrogens does not produce an excess risk of endometrial carcinoma in Finland. (218 refs)

- 79-6569 Numbers of Asbestos Bodies in Urban Patients with Lung Cancer and Gastrointestinal Cancer and in Mat-

ched Controls. (Eng) Churg, A. M. (Dept. Pathology, HSW595, Univ. California Sch. Medicine, San Francisco, CA 94143); War-nock, M. L. *Chest* 76(2): 143-149; 1979.

The numbers of asbestos bodies extracted from the lungs of 103 patients with lung cancer and 50 patients with gastrointestinal malignant neoplasms were compared with the numbers of bodies extracted from the lungs of control patients matched for age, sex, smoking habits, and, in some cases, occupation. All patients were urban dwellers over the age of 40, and none was a primary asbestos worker. No differences in the counts of asbestos bodies were observed between the tested and control populations. The numbers of asbestos bodies did correlate well with occupation; the highest counts were found in male manual laborers. It is concluded that in the urban population studied, the numbers of asbestos bodies alone do not correlate with the presence of pulmonary or gastrointestinal carcinoma. However, uncoated asbestos fibers are also present in the lung, and the possibility that such tumors may be related to the numbers of these fibers in lungs remains to be explored. (25 refs)

- 79-6570 Influence of Dose and Fiber Type on Respiratory Malignancy Risk in Asbestos Cement Manufacturing. (Eng) Weill, H. (Dept. Medicine, Tulane Univ. Sch. Medicine, New Orleans, LA); Hughes, J.; Waggenspack, C. *Am Rev Respir Dis* 120(2): 345-354; 1979.

The risk of respiratory malignancy in relation to duration, degree, and type (fiber) of exposure to asbestos was studied based on a cohort of 5,645 men employed for at least 1 continuous mo before 1970 in either of two cement building materials plants in New Orleans and followed up for at least 20 yr. Cause-specific standard mortality ratios (SMR) increased slightly with degree of exposure, and the SMRs for respiratory system neoplasms exceeded 100 in men exposed to ≥ 101 million particles/ft³-yr (mppcf-yr). There was no excess mortality related to any cause other than respiratory neoplasms. Similar patterns were observed when the number of deaths expected on the basis of Louisiana death rates were used for comparison. Two pleural mesotheliomas were diagnosed, but both patients died prior to the end of the minimum 20-yr follow-up period. In men exposed to <101 mppcf-yr, the SMR for respiratory neoplasms did not change significantly with time since initial exposure, but the SMR increased with time since initial exposure in those exposed to ≥ 101 mppcf-yr. The mean total dust exposure was 164.1 mppcf-yr for the cancer patients in the cohort as compared with 77.8 mppcf-yr for control subjects ($p < 0.005$). The overall pattern of the odds ratio (an estimate of relative risk) was similar to that of the SMR for respiratory malignancy. The SMR for respiratory malignancy in nine duration-by-average-concentration categories generally indicated increasing risk with duration of employment and av concentration. The addition of crocidolite to chrysotile enhanced the risk for respiratory malignancy seen with chrysotile alone, especially in workers exposed intermittently to high concentrations of dust for short periods of time. (22 refs)

- 79-6571 Breast Cancer Mortality and Diet in the United States. (Eng) Gaskill, S. P. (Div. Clinical Epidemiology, Dept. Medicine, Univ. Texas Health Science Center at San Antonio, San Antonio, TX 78284); McGuire, W. L.; Osborne, C. K.; Stern, M. P. *Cancer Res* 39(9): 3628-3637; 1979.

Internationally, breast cancer (BC) mortality is correlated with intestinal lactase sufficiency and dairy product consumption beyond childhood. Within the US, age-adjusted BC mortality is positively

associated with consumption of milk, butter, and total milk fat in regional analyses, and it is associated with milk demand in state-based analyses. BC mortality is also positively associated with demand for total calories, protein, fat, beef, and table fats (butter and margarine), and it is negatively associated with egg demand. Only the associations with milk and egg demand, however, survive when the Southern states are eliminated from the analyses or when either age of first marriage or income is controlled. The associations with milk and egg demand persist despite multiple controls for other dietary and demographic variables, although the association with milk demand loses statistical significance in some second- and third-order partial correlations. The inverse correlation with egg demand is strong but in the opposite direction from what might have been expected from previous studies. The correlation between milk demand and BC mortality, although weaker, is consistent with results from previous studies, and it suggests a possible special role for dairy products in the etiology of BC. (68 refs)

- 79-6572 Breast Cancer in Surinam. (Eng) Brathwaite, A. F. (Academic Hosp. Paramaribo, Paramaribo, Surinam). *Trop Geogr Med* 31(1): 81-85; 1979.

The pathology of malignant lesions of the breast among residents of Surinam during 1964-1976 was studied retrospectively. Breast malignancies were diagnosed in 242 women and no men. The lesions were carcinomas in all but four patients, who had sarcoma. The mean age was 55.1 yr (range, 24-89 yr), and 45% of the patients were from the Creole population. The incidence during the study period was calculated as 9.5/100,000. Lymph node metastases, primarily to the axillary nodes, were confirmed in 85 patients with carcinoma. In the carcinoma patients, 115 tumors were in the left breast, 106 were in the right breast, and 17 were not localized as to side. (2 refs)

- 79-6573 "Incessant Ovulation" and Ovarian Cancer. (Eng) Casagrande, J. T. (Dept. Community and Family Medicine, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033); Pike, M. C.; Ross, R. K.; Louie, E. W.; Roy, S.; Henderson, B. E. *Lancet* 2(8135): 170-173; 1979.

To determine the influence of fertility and oral contraceptive use on the risk of ovarian cancer, a case-control study was made of 150 ovarian cancer patients under the age of 50 and individually matched controls. The risk decreased with increasing numbers of live births, with increasing numbers of incomplete pregnancies, and with the use of oral contraceptives. These three factors can be combined into a single index of protection, "protected time," by considering them all as periods of anovulation. The complement of protected time [ie, "ovulatory age", the period between menarche and diagnosis of ovarian cancer (or cessation of menses) minus "protected time"] was strongly related to risk of ovarian cancer. Other factors found to be associated with increased ovarian cancer risk were obesity, cervical polyps, and gallbladder disease. Women who had an "immediate" intolerance to oral contraceptive use had a fourfold increased risk of ovarian cancer. Seven patients, but no controls, could recall a family history of ovarian cancer. (24 refs)

- 79-6574 Epidemiology of Hepatocellular Adenoma. The Role of Oral Contraceptive Use. (Eng) Rooks, J. B. (Office Population Affairs, Washington, DC); Ory, H. W.; Ishak, K. G.; Strauss, L. T.; Greenspan, J. R.; Hill, A. P.; Tyler, C. W. *JAMA* 242(7): 644-648; 1979.

A case-control study of the association between hepatocellular adenoma (HCA) and use of oral contraceptives (OC's) was conducted by interviewing 79 women with HCA and 220 age- and neighborhood-matched controls. Limited information was obtained for nine additional patients who had died. Women with HCA and hemorrhage have a greater risk of morbidity and death than those with other symptoms. Increasing duration of OC use increases the risk of HCA. Use of OC's with a high hormonal potency and age >30 yr may further increase a woman's risk of HCA. Long-term users of OC's have an estimated annual incidence of HCA of 3.4/100,000. (24 refs)

- 79-6575 Mutagens in the Feces of 3 South-African Populations at Different Levels of Risk for Colon Cancer. (Eng) Ehrlich, M. (Anaerobe Lab., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA 24061); Aswell, J. E.; Van Tassell, R. L.; Wilkins, T. D.; Walker, A. R.; Richardson, N. J. *Mutat Res* 64(4): 231-240; 1979.

The incidence of mutagens in the feces of three South African populations at different risk levels for colon cancer, urban whites (high-risk population) and urban and rural blacks (2 low-risk populations), was determined. Lyophilized fecal samples were extracted with ether, and the mutagenicity of the extracts was determined in the *Salmonella*/mammalian microsome mutagenicity test. Nineteen percent of the samples from the urban whites were mutagenic using *Salmonella typhimurium* strain TA100. This incidence was significantly greater ($p < 0.001$) than the incidence of mutagen excretion in the urban blacks (2%) and rural blacks (0%). This pattern was also obtained using *S. typhimurium* strain TA98. The incidence of mutagen excretion for urban whites was 10%, compared with 5% and 2% for urban and rural blacks, respectively. (36 refs)

- 79-6576 An Analysis of the Mortality of Workers in a Nuclear Facility. (Eng) Gilbert, E. S. (Pacific Northwest Lab., Richland, WA 99352); Marks, S. *Radiat Res* 79(1): 122-148; 1979.

An analysis was made of data from the Hanford nuclear plant in Washington State, where many workers have been employed in jobs involving some exposure to radiation. Mortality from all causes, all cancers, and specific cancer types was related to personnel and exposure data for the population at risk. The mortality of the Hanford workers was first compared with that of the US population and then related to radiation exposure without reference to an outside population. The first analysis showed a substantial "healthy worker effect" and no significantly high standardized mortality ratios for specific disease categories. A test for association of mortality with levels of radiation exposure revealed no correlation for all causes and all cancers. A statistically significant test for trend was obtained for multiple myeloma and cancer of the pancreas, but no evidence of a positive correlation was found for 13 other cancer sites, including those more typically associated with radiation exposure such as myeloid leukemia and lung cancer. The possibility of other occupational exposures and the lack of reliability with respect to the diagnosis of pancreatic cancer must be considered in interpreting these results. The identified correlations resulted from a small number of deaths with exposures >15 rem (roentgen-equivalents-man). The lack of correlation for all cancers and for leukemia is not inconsistent with current estimates of such effects, given the amount of radiation exposure that had been received. (32 refs)

- 79-6577 Endometrial Carcinoma: The Effect of Estrogens. (Eng) Underwood, P. B. (Dept. Obstetrics and

Gynecology, Medical Univ. South Carolina, Charleston, SC 29403); Miller, M. C.; Kreutner, A.; Joyner, C. A.; Lutz, M. H. *Gynecol Oncol* 8(1): 60-73; 1979.

Three hundred seventy-three women with endometrial adenocarcinoma diagnosed at one medical center from August 1967 through February 1977 were studied according to their history of exogenous estrogen intake. Of the patients referred to as "estrogen users," 35% were or had been on some form of estrogen, with only 4% of the total population using estrogen <6 mo. Women with endometrial adenocarcinoma associated with exogenous estrogen ingestion were younger, thinner, and diagnosed at an earlier stage, and they had a more differentiated neoplasm, less myometrial invasion, and a better survival. Birth control pills could be associated with adenocarcinoma in only four of the estrogen users. (10 refs)

- 79-6578 A Catalog of Risks. (Eng) Cohen, B. L. (Dept. Physics and Astronomy, Univ. Pittsburgh, Pittsburgh, PA 15620); Lee, I. S. *Health Phys* 36(6): 707-722; 1979.

Information on risks from various sources was reviewed and converted into loss of life expectancy throughout life and in various age ranges. The risks include radiation, accidents of various types, various diseases, overweight, tobacco, alcohol, drugs, coffee, saccharin, birth control pills, occupational factors, socioeconomic factors, marital status, geography, service in the US armed forces in Vietnam, catastrophic events, energy production, and technology in general. Information is also included on methods for reducing risks, risks in individual actions, "very hazardous" activities, and priorities and perspective. Risks of natural and occupational radiation and exposure to radioactivity from the nuclear industry are compared with those of similar or competing activities. (46 refs)

- 79-6579 Differences in Age and Sex Distributions Among Patients with Non-Hodgkin's Lymphoma. (Eng) Elias, L. (Cancer Res. and Treatment Center, Univ. New Mexico, 900 Camino de Salud, NE, Albuquerque, NM 87131). *Cancer* 43(6): 2540-2546; 1979.

The records of 337 adult patients with non-Hodgkin's lymphoma seen at the Stanford University Medical Center were examined to determine whether there are any relationships between stage and histopathological classification and simple demographic characteristics (age and sex). Patients with Stages I and II disease and diffuse varieties of lymphoma were younger than patients in other categories. An excess of male patients was noted, particularly among younger patients with diffuse lymphoma and Stages I and II disease. Male patients with Stages I and II disease were bimodally distributed with respect to age, with peak numbers of patients occurring in the fourth and sixth decades. This was particularly apparent among patients with diffuse histiocytic lymphoma. (46 refs)

- 79-6580 Bladder Complications in Patients Receiving Cyclophosphamide for Systemic Lupus Erythematosus or Rheumatoid Arthritis. (Eng) Plotz, P. H. (Arthritis and Rheumatism Branch, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Building 10, Room 9N210, Bethesda, MD 20205); Klippel, J. H.; Decker, J. L.; Grauman, D.; Wolff, B.; Brown, B. C.; Rutt, G. *Ann Intern Med* 91(2): 221-223; 1979.

The incidence of bladder complications in patients treated with cyclophosphamide (CP) for nonmalignant inflammatory rheumatic conditions was studied. Among 11 patients with rheumatoid arthritis treated with po CP, two cases of hemorrhagic cystitis and one case of widely metastatic bladder carcinoma without antecedent cystitis occurred. The cancer patient was a 70-yr-old woman who smoked cigarettes and had stopped taking CP 5 yr prior to the diagnosis of cancer. Among 43 lupus erythematosus (LE) cystitis patients treated with po CP, five had acute hemorrhagic cystitis, one of whom developed a papillary transitional cell carcinoma of the bladder. The carcinoma patient had experienced recurrent hematuria during CP therapy, and gross hematuria developed 28 mo after discontinuation of the drug treatment. The expected number of bladder carcinoma cases among the study population was 0.02, and the relative risk ratio was 100. No bladder complications occurred among 12 patients with LE treated with intermittent, iv CP or among 42 patients with lupus nephritis treated with azathioprine or corticosteroids alone. (10 refs)

- 79-6581 Opium: A Potential Urinary Bladder Carcinogen in Man. (Eng) Sadeghi, A. (Dept. Radiation Therapy, Nemazee Hosp., Shiraz, Iran); Behmard, S.; Vesselinovitch, S. D. *Cancer* 43(6): 2315-2321; 1979.

Evidence that opium addiction is a risk factor for cancer of the bladder is presented. A case-control study was made of 99 bladder cancer patients admitted to an Iranian hospital. Cancer patients and controls, matched by age and sex, were analyzed as to their opium and/or cigarette smoking habits. A high correlation between opium addiction and bladder cancer was observed. This correlation was significantly stronger than the one observed in relation to cigarette smoking only. The male:female sex ratio for this cancer site, based on hospitalized cases in Southern Iran, is approx 9:1. The high male:female ratio was attributed to the greater addiction of men to opium. It is concluded that opium and, more likely, its pyrolysis products may be potential bladder carcinogens in humans. (25 refs)

- 79-6582 Colorectal Carcinoids in South India. (Eng) Radhakrishnan, S. (Dept. Pathology, Thanjavur Medical Coll., Thanjavur, India); Subramoniam, S. *Trop Geogr Med* 31(1): 63-67; 1979.

The incidence of colorectal carcinoids among southern Indians was studied during 1965-1974. Seventeen men and three women with colorectal carcinoids were identified. They ranged in age from 20-65, but most were between 30 and 55. The most common site of involvement was the rectum, followed by the cecum, ascending colon, and hepatic flexure. Eight patients noticed a lump in the abdomen, 1 experienced recurrent intussusception, 10 had bloody stools, 9 had pain and vomiting, and 2 developed ascites. None had a carcinoid syndrome. Except for one case, all growths were single. The tumors were predominantly submucosal, and the majority were >2 cm in diameter. Only eight appendicular carcinoids were observed during the study period. The high incidence of colorectal carcinoids in this series of patients suggests a racial difference in organ susceptibility. (10 refs)

- 79-6583 Lung Cancer in Greater Bombay: Correlations with Religion and Smoking Habits. (Eng) Jussawalla, D. J. (Bombay Cancer Registry, Indian Cancer Society, Bombay, India); Jain, D. K. *Br J Cancer* 40(3): 437-448; 1979.

The resident population of Greater Bombay was analyzed for lung cancer incidence and other variables of possible significance to lung cancer incidence. During a 10-yr period from 1964-73, 2,177 lung cancer cases (1,861 males, 316 females) were registered from a population pool consisting of 5.24 million persons (3.07 million males, 2.17 million females). The av annual incidence of lung cancer was 13.6 per 10⁵ males but only 3.3 per 10⁵ females (age-adjusted to the Standard World Population). The incidence in non-Parsi males (14.0) was almost double the figure in Parsi males (6.8). However, there was no significant difference in incidence between non-Parsi (3.8) and Parsi females (3.3). Time-trend analyses did not reveal statistically significant differences in lung cancer incidence in any particular age group, male or female. The data from death certificates for the same 10-yr period showed that the age-adjusted rates were 11.0 and 3.3 per 10⁵ for males and females, respectively in the total population. In a retrospective study, 792 males with lung cancer (4.2% of 1,861 male cancer patients) for whom detailed smoking history was available were matched for age and community with randomly selected controls, obtained from the voters list of the Greater Bombay Corporation; and significant statistical association was found between tobacco smoking and lung cancer. All smokers appear to be at high risk (16.8) compared with nonsmokers. The relative risk for bidi smokers was 19.3, even higher than that for cigarette smokers (8.6). Hindu, Muslim and Christian smokers are apparently at identical risks. A dose-response relationship was found for bidi and cigarette smokers. (11 refs)

- 79-6584 Tar Exposure in Tobacco-associated Lung and Bladder Cancer. (Ger) Kunze, M. (Hygiene-Institut, Arbeitsgruppe Sozialmedizin der Universität, Kinderspitalgasse 15, A-1095 Vienna, Austria); Vutuc, C. *Munch Med Wochenschr* 121(32/33): 1041-1042; 1979.

A questionnaire study of smoking history was carried out in 200 men with lung cancer (group I) and 150 men with bladder cancer (group II). The av ages of men in groups I and II were 63.2 yr and 68.7 yr, respectively. Ninety-five percent of those in group I smoked cigarettes vs 87% of those in group II ($p < 0.01$). Cigarettes of high tar content (>25 mg) were currently smoked more frequently by group II patients than by group I ($p < 0.01$) patients. Group II patients had smoked an av of 2.5 yr longer than group I patients. These observations suggest that the critical amount of exposure to smoking producing bladder cancer is higher than that leading to lung cancer. The use of high tar cigarettes was more prevalent in both groups, compared with the general population. The av tar content of cigarettes produced in Austria was 33.7 mg in 1960, and declining to 18.3 mg in 1975. Since 1965, the av content has been <25 mg. Evidence for possible exposure to carcinogens at work was found in only 6% of the patients, indicating that smoking is a more important cause of bladder and lung cancer in Austria than is occupational carcinogen exposure. (8 refs)

- 79-6585 Mortality in Gold and Coal Miners in Western Australia with Special Reference to Lung Cancer. (Eng) Armstrong, B. K. (Public Health Dept., Western Australia, Australia); McNulty, J. C.; Levitt, L. J.; Williams, K. A.; Hobbs, M. S. *Br J Ind Med* 36(3): 199-205; 1979.

Cohorts of 1,974 gold miners and 213 coal miners in Western Australia were surveyed and followed up for 13-14 yr for respiratory symptoms, smoking habits, occupational history, and radiographic evidence of pneumoconiosis. Overall, neither group had a significantly higher mortality rate than expected from the experience of Western Australian men in general. Lung cancer mortality was relatively high in the gold miners (59 deaths observed,

40.8 expected) but weakly and inconclusively related to the extent of their underground mining experience. The excess of lung cancer in the gold miners may be attributable to cigarette smoking, which was more common among these miners (66.3%) than among the coal miners (58.7%) or the other men in Western Australia (53.2%). Radiographic evidence of silicosis was present in 21.7% of the gold miners but did not appear to have contributed substantially to their mortality. The coal miners showed a lower than expected rate of lung cancer but an excess of deaths from all other forms of cancer (11 observed, 5.6 expected). This excess was not specific to any one cancer site and could not be explained readily. (31 refs)

79-6586 Alimentary Tract Cancer in Australia in Relation to Diet and Alcohol. (Eng) McMichael, A. J. (Div. Human Nutrition, Commonwealth Scientific and Industrial Res. Organization, Kintore Ave., Adelaide, S. Australia 5000, Australia). *Nutr Cancer* 1(3): 82-89; 1979.

Time trends in cancer mortality and in the consumption of major foods and alcohol in Australia were examined. Although stomach cancer mortality has declined by about 65% since the 1920s, esophageal cancer mortality, initially steady, has subsequently declined and then increased again. The male/female ratios for stomach and esophageal cancer are 4:1 and 2:1, respectively. The declines in risk for both cancers occurred between successive generations. The generation born around 1870 experienced peak mortality from esophageal cancer at each age, whereas the generation immediately following initiated the decline at each age. The recent upswing in rates has been stronger among young age groups, suggesting the beginning of a second, generation-based increase. Consumption of alcoholic beverages was moderately high during 1910-1915, markedly lower through the 1920s, and has increased steadily since World War II. Since the 1930s, there has been about a 15% reduction in pulses and consumption of cereals, roots, and tubers. Refrigeration has improved, increasing the consumption of fruits and vegetables, and probably vitamins A and C. There has been a modest decline in dietary fiber intake but no increase in total or saturated fat or beef consumption. Allowing for a 10-20 yr cancer latency period, the time trends in the sex ratios of colorectal cancer mortality in Australia, England, and Wales have generally followed the beer consumption trends. For rectal cancer in men, the percentage change in mortality follows closely the percentage change in the immediately preceding beer consumption. The initially high incidence of colon and rectal cancer among migrants from Scotland and England declined with time spent in Australia, whereas the initially low incidence among migrants from Greece and Yugoslavia increased after migration to Australia. Stomach cancer risk generally decreased in migrants to Australia. Socioeconomic differences in gastrointestinal cancer risk within Australia are also apparent. (25 refs)

79-6587 The Association of Parity and Marital Status with the Development of Ovarian Carcinoma: Clinical Implications. (Eng) Demopoulos, R. I. (Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY 1016); Seltzer, V.; Dubin, N.; Gutman, E. *Obstet Gynecol* 54(2): 150-155; 1979.

During 1962-1977, 327 patients with ovarian carcinoma were compared with matched controls to determine the association of parity and marital status with the development of this neoplasm. The relative risk of developing ovarian cancer was 2.31 times greater in nulliparous women than in parous women, and among parous women, the risk increased significantly with lower parity. The association with parity was generally similar in younger and older women and among patients from both low and high

socioeconomic levels. There was also a highly significantly greater risk of ovarian cancer among "never-married" women than among "ever-married" women, but there were no significant associations with religion. (25 refs)

79-6588 A Statistical Study of Sarcoma Complicating Paget's Disease of Bone in Three Countries. (Eng) Brackenridge, C. J. (National Res. Inst. Gerontology and Geriatric Medicine, Mount Royal Hosp., Parkville 3052, Australia). *Br J Cancer* 40(2): 194-200; 1979.

Data concerning sex, age at presentation and anatomical site of sarcoma complicating Paget's disease of bone were recorded from the literature for white patients in Australia, the United Kingdom and the US over the period 1918-77. Evidence is presented to suggest that sex and tumor-site distributions are free from bias, except, possibly, for the skull. There was a male predominance for all sites except the skull, for which the odds ratio of sarcoma compared with other locations was more than twice as high for women than for men. No national differences emerged in the sex ratio of the patients. In Australia, a latitudinal effect was observed. Although the percentage of men with uncomplicated Paget's disease was essentially constant, those with sarcoma showed a decrease with increase in latitude from Queensland to Victoria. This was attributable to tumors of the skull. Patients with bone involvement above the waist were significantly younger than those with affected feet, legs, or pelvic girdle. (28 refs)

79-6589 Childhood Lymphoma in Southern Iran. (Eng) Haghighi, P. (Dept. Pathology, Pahlavi Univ., Shiraz, Iran); Mostafavi, N.; Dezhbakhsh, F.; Ariazad, M.; Ghassemi, H.; Cook, A.; Salmassi, S.; Nabizadeh, I.; Asvadi, S. *Cancer* 44(1): 254-257; 1979.

A study was made of 81 childhood lymphomas diagnosed in the Department of Pathology of the Pahlavi University Medical Center, Shiraz, Iran. These disorders encompassed all histologically diagnosed childhood lymphomas from the Fars Province, Southern Iran, over a 14-yr period (1963-1976). There was a 3:1 male predominance and a 1:4 child/adult ratio. Peripheral lymphadenopathy at the initial physical examination was almost twice as common as deep node involvement. Comparison of cumulative and age-standardized (to world population) incidence rates with those of selected tumor registries in various continents revealed a higher rate of both non-Hodgkin's and Hodgkin's lymphoma in this region relative to some of the Western countries. The incidence rates were, in general, intermediate between Western populations on the one hand and some South American, African, and Asian populations on the other. Hodgkin's disease accounted for 64% (males) and 88% (females) of the lymphomas, and mixed cellularity was the commonest histologic subtype. Histologically, almost all the non-Hodgkin's lymphomas were diffuse at the time of diagnosis. (11 refs)

See also:

*(Rev.) 79-6011, 79-6022, 79-6025, 79-6026, 79-6029, 79-6042, 79-6046, 79-6047, 79-6051, 79-6053, 79-6054, 79-6057, 79-6062, 79-6080, 79-6094, 79-6097, 79-6098, 79-6099, 79-6100, 79-6101, 79-6102, 79-6104, 79-6105, 79-6106, 79-6107, 79-6108, 79-6109, 79-6110, 79-6111, 79-6112, 79-6113, 79-6114, 79-6115, 79-6116, 79-6117, 79-6118, 79-6119, 79-6120, 79-6121, 79-6122, 79-6123, 79-6124, 79-6125, 79-6126, 79-6127.

*(Chem.): 79-6155, 79-6182, 79-6217, 79-6222.

*(Phys.): 79-6371.

*(Path.): 79-6540, 79-6550.

MISCELLANEOUS

- 79-6590 Physico-chemical Studies of Isolated Chromatin Compared with In Situ Chromatin After Partial Hepatectomy in the Rat. (Eng) Miller, P. (Div. Biophysics, Temple Univ. Graduate Sch., Philadelphia, PA 19140); Linden, W. A.; Nicolini, C. *Z Naturforsch [C]* 34(5/6): 442-448; 1979.

The partially hepatectomized rat was used as an in vivo model to study changes in liver cell chromatin (CT) conformation after stimulation of the cells to proliferate. CT was isolated from rat liver cells at 0, 3, 5, 11, 18, and 24 hr following partial hepatectomy. Consistent with findings in cultured cells stimulated to proliferate, there was an increase in the molar ellipticity of CT measured at 276 nanometers, and a decrease in the thermal stability of CT 3-8 hr after surgery. These events occurred prior to the onset of DNA synthesis. The early changes between non-proliferating (G_0) and proliferating (G_1) cells, as well as later CT conformational changes observed at S and G_2 mimicked changes in template activity. The results with sheared and unsheared CT (both with in vitro and in vivo systems) proved that structural and functional changes can be caused by even the slightest shearing during CT preparation, suggesting the loss of native CT organization. To eliminate this problem, experiments were also conducted using CT in situ. A flow cytometer (FCM) was used to study unfixed liver cell suspensions stained with ethidium bromide (EB). Fluorescence was measured in the green spectral range after the addition of increasing amounts of EB. The same alteration in CT conformation was best detected using low molar ratios of EB per unit DNA, because of the greater fluorescence emission in G_1 than in G_0 cells. These correlated studies demonstrate that the same changes controlling CT organization in situ are detected also in the tertiary-quaternary structure of isolated CT. These changes in CT conformation are macromolecular events related to cell proliferation both at the G_0 - G_1 and G_1 -S transitions. (27 refs)

- 79-6591 A Hydroxylapatite Batch Assay for Quantitation of Cellular DNA Damage. (Eng) Kanter, P. M. (Dept. Experimental Therapeutics, Grace Cancer Drug Center, New York State Dept. Health, Roswell Park Memorial Inst., Buffalo, NY 14263); Schwartz, H. S. *Anal Biochem* 97(1): 77-84; 1979.

DNA damage was measured quantitatively by a batch elution procedure based on alkaline unwinding of cellular DNA and separation of single-stranded from duplex forms by step elution from hydroxylapatite with phosphate formamide. The method is rapid, permits large numbers of samples to be handled simultaneously, and consistently yields recoveries of >95% of total chromatographed DNA. Because as many as 1×10^7 cells per batch may be analyzed, quantitation of the eluted DNA by nonradioactive methods is feasible. The method is standardized with respect to the unwinding constant β , the alkaline DNA unwinding unit Mn_0 , and the DNA-damaging efficiency of ionizing irradiation. (19 refs)

- 79-6592 Metabolic Utilization of Arginine by Acute Myeloid Leukemia Cells. (Pol) Hansz, J. (Klinika Hematologii, Instytutu Chorob Wewnętrznych Akademii Medycznej, ul. Szkolna 8/12, 61-833 Poznan, Poland). *Pol Arch Med Wewn* 61(2): 113-120; 1979.

The metabolism of ^{14}C -arginine by acute myeloid leukemia cells and by normal granulocytes was compared. The results showed that the leukemic cells incorporated much more of the amino acid into their protein than the normal granulocytes. The highest activity was demonstrated by cells from the blastic crisis of chronic myeloid leukemia. The amount of ^{14}C -arginine incorporated into the leukemic cell protein depended to a considerable extent on the degree of cell maturation; ie, the blast cells incorporated more than the mature WBC. The results indicate that leukemic transformation is associated with an increased metabolic requirement for arginine. (16 refs)

- 79-6593 Lectin-mediated Agglutination of Murine Lymphoma Cells. Cell Surface Deformability and Reversibility of Agglutination by Saccharides. (Eng) Nicolson, G. L. (Dept. Developmental and Cell Biology, Univ. California, Irvine, CA 92717); Poste, G. *Biochim Biophys Acta* 554(2): 520-531; 1979.

The secondary effects occurring during the lectin-mediated cell agglutination of a murine S49 lymphoma cell line that grows as isolated cells in suspension and does not establish cell-to-cell adhesions were studied. When S49 cells were agglutinated by *Ricinus communis* 1 lectin, agglutination occurred in a dose- and temperature-dependent fashion. The multicell aggregates thus formed could be dispersed by treatment with lactose [50-100 millimolar (mM)], but only if it was added immediately after removal of the lectin. The irreversibility of S49 cell agglutination was dependent on time, temperature, and lectin concentration; and its onset was correlated with ultrastructural deformations of adjacent cell surfaces and increases in the proportion of adjacent cell surface areas in close apposition with multicell aggregates. Cytochalasin B (CB, 10-20 μ g/ml) enhanced S49 agglutination by *R. communis* 1 agglutinin, whereas vinblastine sulfate (VS, 1-10 μ M) and preincubation of the S49 cells with sodium fluoride (SF, 5 mM) plus sodium azide (SA, 2 mM) had no effect. VS or VS plus CB inhibited lactose dispersal of the S49 multicell aggregates, while SF plus SA enhanced hapten reversibility. The onset of agglutination irreversibility correlated with cell surface deformation in the drug-treated cells. Cell aggregates that were more readily reversible by lactose were unchanged or less deformed, whereas those treated with CB plus VS were more deformed compared with controls. The data suggest a role for cell surface deformability as an important secondary effect during lectin-mediated cell agglutination of S49 cells. (40 refs)

- 79-6594 Sequence Complexity of Transcribed Unique DNA Sequences in Mouse P815 Mastocytoma Cells. (Ger) Boehm, T. L. (Zentrum der Biologischen Chemie, Universitat Frankfurt am Main, Theodor-Stern-Kai 7, 6000 Frankfurt am Main 70, W. Germany); Drahovsky, D. *Z Naturforsch [C]* 34(5/6): 436-441; 1979.

The sequence complexity of nuclear RNA (nRNA) from mouse liver, spleen, and mastocytoma P815 cells was measured by hybridization of nRNA to unique DNA sequences of the P815 cells. Assuming asymmetrical transcription, the complexities of the transcripts were 2.8×10^6 nucleotides for the P815 mastocytoma, 4.3×10^6 for the spleen, and about 5.3×10^6 nucleotides for the liver. (13 refs)

- 79-6595 **Enhancing Effect of Thyroxine on Tumor Growth and Metastases in Syngeneic Mouse Tumor Systems.** (Eng) Kumar, M. S. (Dept. Immunopathology, Cleveland Clinic Foundation, Cleveland, OH 44106); Chiang, T.; Deodhar, S. D. *Cancer Res* 39(9): 3515-3518; 1979.

The effect of synthetic L-thyroxine (TX) treatment on tumor growth and metastases resulting from tumor implants on the hind feet of mice was studied in two syngeneic systems. In control untreated A/Jax mice, sarcoma 1 at day 4 after implantation had an av tumor wt of 582 ± 60 (SD) mg and showed an incidence of 57% metastases to regional popliteal nodes and 5% metastases to the thymus. In contrast, the TX-treated group ($40 \mu\text{g}/\text{mouse}$ sc, 5 times/wk for 1 mo) had an av tumor wt of 808 ± 56 mg ($p < 0.001$), and metastases to popliteal nodes and thymus were 90% and 35%, respectively. In another syngeneic tumor system, Lewis fibrosarcoma was implanted in C57BL/6J mice, and the tumor wt and metastatic index (derived from the number and size of the pulmonary tumor foci) were determined at Day 28. Again, the TX-treated group showed a significant enhancement of tumor growth and metastatic index. The mean tumor wt in the treated group was 835 ± 26 mg (control, 694 ± 25 mg; $p < 0.005$), and the metastatic index was 84 ± 29 (control, 30 ± 25 ; $p < 0.001$). Induced hypothyroidism (treatment with ^{131}I , $100 \mu\text{Ci}/\text{mouse}$ ip) showed the reverse effect on both tumor systems. These results suggest that both tumor systems are dependent on thyroid hormones for their growth and spread. (22 refs)

- 79-6596 **Correlation of Glycosylation in a Membrane Protein with a Molecular Weight of 150,000 with Tumorigenic Property of Rat Fibrosarcoma Variants.** (Eng) Koyama, K. (Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Nudelman, E.; Fukuda, M.; Hakomori, S. *Cancer Res* 39(9): 3677-3682; 1979.

An attempt was made to correlate the status of glycosylation in a 150,000-dalton membrane protein with the tumorigenicity of rat fibrosarcoma variants. Four clonal variants with differing degrees of tumorigenicity and intercellular adhesiveness were isolated from a tumor induced by methylcholanthrene in inbred Donryu rats. Variant clones G and Z were characterized by an extremely low tumorigenicity, in contrast to the high tumorigenicity of the original clone A and variant clone P. P was highly tumorigenic in ascites form when inoculated ip, but its tumorigenicity was minimal when inoculated sc. Under the scanning electron microscope, sharp, well-developed microvilli were observed on the surface of Z and G, in contrast to the smooth blebs found on the surface of A and P. G cells and, to a lesser extent, Z cells showed a remarkable side-by-side adherence, thereby forming a wormlike shape and sharing a common cell coat. A and P were not adherent. Protein and glycoprotein profiles of these variant cell lines were studied by the following surface-labeling techniques: lactoperoxidase-catalyzed [^{125}I]iodination, galactose oxidase- NaB^3H_4 , periodate- NaB^3H_4 , and by metabolic labeling with precursor sugars. The variant cell lines showed a remarkable difference in degree of sialylation in one glycoprotein species with a relative mol wt of 150,000, whereas the profiles of other proteins and glycoproteins were indistinguishable among the lines. The status of glycosylation in this unique 150,000-dalton glycoprotein may reflect the tumorigenicity of the four variant isolates. (29 refs)

- 79-6597 **Synthesis of α -Fetoprotein, Albumin, and Transferrin in Continuous Murine Hepatoma Cell Lines.** (Rus) Aleksanian, Iu. T. (Lab. Molecular Basis Immunogenesis, Inst.

Experimental Biology, Erevan, USSR). *Biull Eksp Biol Med* 88(7): 76-77; 1979.

This study was designed to determine whether murine hepatoma XXIIa cells continuously cultured in vitro retain the capability to synthesize marker serum proteins. An indirect radioimmunoassay revealed that 5-yr cultures contained albumin and transferrin, but no α -fetoprotein (AFP). Eight-yr cultures contained only transferrin. Inoculation of C3HA mice with both 5- and 8-yr cells (10^5 - 10^6 cells/mouse) resulted in tumor development, which indicated that continuously cultured cells retained tumorigenic activity. The serum of mice inoculated with 5-yr cells contained AFP, but not the serum of mice inoculated with 8-yr cells. These findings indicate that the loss of AFP in 5-yr cultures is reversible. (11 refs)

- 79-6598 **Repression, Derepression, Transinhibition, and Trans-stimulation of Amino Acid Transport in Rat Hepatocytes and Four Rat Hepatoma Cell Lines in Culture.** (Eng) Kelley, D. S. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Potter, V. R. *J Biol Chem* 254(14): 6691-6697; 1979.

The effects of amino acid depletion and supplementation on the transport of amino acids in four hepatoma cell lines (HTC, H-35, 7777, and 8994) were compared with the effects in hepatocytes. In both the hepatocytes and hepatoma cell lines, amino acid starvation caused a five- to eightfold increase in the sodium-dependent transport of 2-aminoisobutyric acid (AIB) without affecting the sodium-independent transport. The hepatoma cell lines reached the max level of AIB uptake within 12 hr of amino acid starvation, maintained this level for 12 hr, and showed a considerable increase in the uptake of leucine. The hepatocytes reached the max level of AIB uptake within 24 hr of amino acid starvation, maintained this activity for 24 hr, and showed only a moderate increase in leucine uptake. The increase in the activity of the A system resulting from amino acid starvation could be blocked by actinomycin D or cycloheximide. AIB added to the starvation medium completely blocked the increase in the activity of the A system in hepatocytes and three of the hepatoma lines, but there was a slight increase in AIB uptake by H-35. In both the hepatocytes and hepatoma lines, the increase in activity of the A system was due to derepression and to release from transinhibition of the transport system. Conversely, the decrease in the activity of the A system caused by the addition of amino acids to the starved cultures was due to repression and transinhibition. (23 refs)

- 79-6599 **Two Polypeptide Changes Associated with Butyric Acid Resistance and the Neoplastic State of Syrian Hamster Cells.** (Eng) Leavitt, J. (Div. Virology, Bureau Biologics, Food and Drug Admin., Bethesda, MD 20014). *Biochim Biophys Acta* 563(1): 227-239; 1979.

Qualitative polypeptide differences between parental Syrian hamster embryo cells and nine independently established neoplastic cell lines transformed by chemical carcinogen treatment, virus infection, or an unknown spontaneous event were examined. Although no perfect correlation with a specific polypeptide change was found, two polypeptide changes, occurring independently or simultaneously, appeared to be consistently associated with expression of neoplasticity. One polypeptide species designated τ , having an isoelectric point of 4.6 and a mol wt of 60,000, was lost or physically altered in all but one of these transformed cell lines; a second polypeptide species designated ν , having an isoelectric point of 5.5 and a mol wt of 42,000, appeared in highly tumorigenic chemically transformed cell lines and in two

virally transformed cell lines. A butyric acid supplement, used as a selective agent for butyric acid-resistant cells, was employed to identify and isolate in a single step nascent neoplastic clonal lines transformed by ethyl methanesulfonate. These cell lines exhibited alterations in τ or ν . The changes observed in τ were consistent with those expected to result from a somatic mutation in the structural gene coding for τ ; however, the alterations in τ could also be governed by a posttranslational process. These findings suggest that alterations in the expression of at least two major polypeptide species, τ and ν , are closely associated with primary steps in the neoplastic transformation of Syrian hamster cells, irrespective of the nature of the transforming agent. (15 refs)

- 79-6600 Histone Acetylation in CV-1 Cells Infected with Simian Virus 40. (Eng) La Bella, F. (Lab. Cell Biology

CNR, Via Romagnosi 18A, 00196 Rome, Italy); Vidali, G.; Vesco, C. *Virology* 96(2): 564-575; 1979.

The histone acetylation of host cell chromatin was compared with that of intracellular 70S minichromosomes in CV-1 monkey kidney cells infected with simian virus 40 (SV40). The degree of acetylation in the histones of cell chromatin did not substantially increase after infection; the 70S minichromosomes contained histones that were not as highly acetylated as those contained in virions, but more acetylated than those associated with the infected cell chromatin. The rate of acetylation, as measured by [3 H]acetate uptake, appeared to be nearly equal for the histones associated with viral and cellular DNA. The acetyl groups incorporated by the 70S histones, however, were retained in larger proportion compared with those incorporated by the host histones. (32 refs)

Author Index

- Abbott, J., 79-6500
Abe, S., 79-6522
Abercrombie, M., 79-6091
Abrahamova, J., 79-6510
Abrahams, P. J., 79-6355
Abrahamson, S., 79-6068
Achong, B. G., 79-6428
Adelstein, A. M., 79-6557
Adelstein, P., 79-6558
Adolf, W., 79-6189
Agarwal, R. A., 79-6307
Aizenberg, B., 79-6461
Aldershoff, W. G., 79-6181
Aleksanian, Iu. T., 79-6597
Alexander, S. S., 79-6516
Alferov, A. N., 79-6311
Allegretti, N., 79-6161
Allen, J. A., 79-6303
Allfrey, V. G., 79-6177
Allison, A. C., 79-6102
Allison, D. P., 79-6444
Alpass, P. R., 79-6499
Almendral, A. C., 79-6123
79-6125
Alsabti, E. A., 79-6088
Altenburg, L. C., 79-6238
Althoff, J., 79-6544
Alumets, J., 79-6539
Amadori, G., 79-6511
Ambrose, K. R., 79-6081
Ames, B. N., 79-6002, 79-6046
Amiri, G., 79-6563
Ancona, E., 79-6511
Andersen, H., 79-6524
Anderson, C. W., 79-6452
Anderson, L. M., 79-6232
Anderson, P. S., 79-6345
Andersson, Y., 79-6142
Ando, K., 79-6493
Andrews, A. W., 79-6202
Andzhaparidze, O. G., 79-6227
Ansari, G. A., 79-6337
Ansley, C. M., 79-6190
Aoki, Y., 79-6188
Apfelzweig, R. A., 79-6358
Aposhian, H. V., 79-6437
Arai, M., 79-6188
Aramesh, B., 79-6563
Arany, I., 79-6187
Argyarakis, M. P., 79-6159
Ariazad, M., 79-6589
Arlett, C. F., 79-6355
Armiger, W. G., 79-6519
Armstrong, B. K., 79-6029
79-6585
Armuth, V., 79-6189, 79-6266
Arnabaldi, A., 79-6287
Ashendel, C. L., 79-6274
Asp, N. G., 79-6176
Asvadi, S., 79-6589
Aswell, J. E., 79-6575
Atfield, G., 79-6477
Aune, T., 79-6016, 79-6167
79-6235
Austin, F. C., 79-6509
Autrup, H., 79-6315
Avakova, A. N., 79-6227
Azarnoff, D. L., 79-6153
Babbar, O. P., 79-6463
Badsberg, E., 79-6524
Bahary, C., 79-6567
Bahna, L., 79-6330
Bailey, D. M., 79-6301
Baker, D. T., 79-6346
Bala, R., 79-6482
Baldwin, J. A., 79-6558
Baldwin, R. W., 79-6039
79-6310, 79-6507
Balk, S. D., 79-6385
Baltimore, D., 79-6403
Banerjee, S., 79-6150
Bannasch, P., 79-6215
Barbason, H., 79-6193
Barbolini, G., 79-6553
Bardini, R., 79-6511
Barker, C. L., 79-6290
Barnes, R. D., 79-6404
Barr, S. M., 79-6437
Bartsch, H., 79-6165, 79-6293
Baserga, R., 79-6449
Bases, R., 79-6466
Bassin, R. H., 79-6416
Battaglia, S., 79-6553
Baudhuin, P., 79-6229
Bauer, H. G., 79-6176
Baum, J. W., 79-6070
Baumal, R., 79-6492
Baumgarten, I., 79-6506
Baumler, A., 79-6237
Beard, C. M., 79-6217
Becci, P. J., 79-6200
Becker, F. F., 79-6172
Bednar, B., 79-6521
Behmard, S., 79-6581
Bekesi, G. J., 79-6476
Bell-Thomson, J., 79-6537
Benda, P., 79-6321
Benes, V., 79-6109
Benesova, M., 79-6330
Benjamin, T. L., 79-6438
Benjers, B. M., 79-6416
Benz, E. W., 79-6413
Beral, V., 79-6560
Berczi, I., 79-6502
Berenblum, I., 79-6189, 79-6266
Berget, S. M., 79-6453
Bergstrom, I., 79-6155
Bernfeld, P., 79-6284
Berns, A., 79-6405
Berry, D. L., 79-6327
Bertsch, S., 79-6275
Betz, E. H., 79-6193
Bhatti, A. R., 79-6455
Bianchi, A., 79-6287
Biberfeld, P., 79-6503
Biemann, K., 79-6182
Bingham, S., 79-6559
Biran, H., 79-6505
Bird, C. C., 79-6526
Bishop, J. M., 79-6380
Bjeldanes, L. F., 79-6160
Black, S. J., 79-6472
Blair, D. G., 79-6400
Blalock, J. A., 79-6547
Blasecki, J. W., 79-6448
Bloching, H., 79-6018
Blumenfeld, W., 79-6474
Bock, F. G., 79-6114
Boehm, T. L., 79-6156, 79-6594
Boethius, G., 79-6155
Boffa, L. C., 79-6177
Bohmalk, G. L., 79-6376
Bojan, F., 79-6187
Bonse, G., 79-6151
Boobis, A. R., 79-6318
Boone, C. W., 79-6509
Bootsma, D., 79-6355
Bornkamm, G. W., 79-6428
Borzsonyi, M., 79-6057
Bos, R. P., 79-6323
Bosslet, K., 79-6484
Bottger, M., 79-6417
Botticelli, A. R., 79-6553
Bottin, M. C., 79-6169
Boutwell, R. K., 79-6274
Boyd, D. R., 79-6017
Boyd, M. R., 79-6219
Boyd, S. C., 79-6219
Boyse, E. A., 79-6500
Bracken, W. M., 79-6327
Brackenridge, C. J., 79-6588
Brackman, K. H., 79-6451
Brackmann, K. H., 79-6454
Bradlaw, J. A., 79-6249
Bradley, W. A., 79-6247
Bralow, S. P., 79-6221, 79-6222
Brathwaite, A. F., 79-6572
Breg, W. R., 79-6487
Brendel, M., 79-6191
Bresnick, E., 79-6312
Brewen, J. G., 79-6035
Brewer, P. P., 79-6392
Brockhaus, A., 79-6054
Bronzetti, G., 79-6243
Brookes, P., 79-6336
Brostrom, C. O., 79-6164
Brostrom, M. A., 79-6164
Brouns, R. E., 79-6323
Brown, B. C., 79-6580
Brown, C. C., 79-6200
Brown, C. E., 79-6351
Brown, H. M., 79-6317
Brown, S., 79-6422
Brozman, M., 79-6218
Brugge, J. S., 79-6382, 79-6386
Brun, G., 79-6165
Brychey, T., 79-6013
Bucker, M., 79-6316
Buckley, J. D., 79-6170
Budingier, J. M., 79-6232
Buening, M., 79-6017
Buening, M. K., 79-6308
Buick, R. N., 79-6090
Bulay, O., 79-6214
Buldakov, L. A., 79-6373
79-6375
Burden, P. M., 79-6289
Burkitt, D. P., 79-6099
Burns, G. F., 79-6525
Butcher, E. C., 79-6469
Butel, J. S., 79-6395, 79-6445
Butler, M. A., 79-6254
Byers, J. F., 79-6527
Cagen, S. Z., 79-6147
Caldwell, E. H., 79-6519
Camus, A. M., 79-6165
Canfield, R. E., 79-6533
Cantilena, L. R., 79-6147
Capel, I. D., 79-6339
Capel, P. J., 79-6496
Cardiff, R. D., 79-6396
79-6397
Carlberg, F. W., 79-6033
Carpenter, J. G., 79-6362
Carroll, K. K., 79-6300
Carruthers, C., 79-6237
Carson, G. A., 79-6182
Cartas, M. A., 79-6451, 79-6454
Casagrande, J. T., 79-6573
Casale, V., 79-6563
Casida, J. E., 79-6002, 79-6056
Casterline, J. L., 79-6249
Cavelier, C., 79-6169
Cawley, J. C., 79-6525
Ceilley, R. I., 79-6473
Cervenka, J., 79-6143
Chait, M. M., 79-6550
Chan, H. W., 79-6410, 79-6434
Chanet, R., 79-6163
Chang, E. H., 79-6410
Chang, R. L., 79-6017, 79-6304
79-6308, 79-6334
Chang, S. K., 79-6245
Chebotarev, V. F., 79-6311
Chen, T. C., 79-6247
Chenpick, O. F., 79-6175
Chernozemsky, I. N., 79-6285
Chew, H., 79-6160
Chiang, T., 79-6595
Chien, Y. H., 79-6415
Chilvers, C., 79-6560
Chiric, E., 79-6409
Chirigos, M. A., 79-6478
Chouroulinkov, I., 79-6309
Chovil, A. C., 79-6053
Chu, K. C., 79-6541
Churg, A. M., 79-6569
Chute, R. N., 79-6351
Cihak, R., 79-6260
Clymer, R., 79-6408
Coffman, R. L., 79-6469
Coggin, J. H., 79-6081
Cohen, A. J., 79-6066
Cohen, A. M., 79-6513
Cohen, B. I., 79-6208
Cohen, B. L., 79-6578
Cohen, G. M., 79-6327, 79-6331
79-6332
Cole, D. A., 79-6231
Cole, T. J., 79-6559
Collett, M. S., 79-6382
Colombatti, A., 79-6405
Colter, J. S., 79-6464
Comoglio, P. M., 79-6388
Concon, J. M., 79-6258
Connell, J. R., 79-6319
Conney, A. H., 79-6015, 79-6017
79-6304, 79-6308, 79-6334
Cook, A., 79-6589
Cook, J. L., 79-6458, 79-6501
Coombs, M. M., 79-6303
Corcoran, G. B., 79-6007
Cornelissen, I. M., 79-6496
Cornfield, J., 79-6033
Costa, M., 79-6499
Coulomb, B., 79-6321
Craddock, V. M., 79-6190
Craig, A. W., 79-6170
Crawford, D. H., 79-6428
Crawford, E., 79-6462
Crespi, M., 79-6563
Croce, C. M., 79-6406, 79-6449
Crombie, I. K., 79-6556
Crossen, P. E., 79-6353
Crouch, N. A., 79-6418
Crummett, W. B., 79-6012
Cubilla, A., 79-6508
Cucos, S., 79-6112
Cudkowicz, G., 79-6468
Curtis, G., 79-6295
Czarnecka, K., 79-6561
D'Adamo, A. C., 79-6533
Dadey, B., 79-6475
Daffara, P., 79-6287
Dahlqvist, A., 79-6176
Damjanov, I., 79-6089
Daniel, J. W., 79-6006
Das, G. C., 79-6444
Das, G. D., 79-6210
Davey, F. R., 79-6482
Davidson, N., 79-6415
Davies, P. J., 79-6383
Daynes, R. A., 79-6494
De Flora, S., 79-6157
de la Pena de Torres, E.
79-6111
De Larco, J. E., 79-6267
de-The, G., 79-6127
De Waal, R. M., 79-6496
Decker, J. L., 79-6580
DeFeo, D., 79-6277
Delpino, A., 79-6192
Demant, P., 79-6405, 79-6514
Demopoulos, R. I., 79-6587
Den Engelse, L., 79-6184
Deodhar, S. D., 79-6595
Derbes, V. J., 79-6527
Deschner, E. E., 79-6221
79-6222
Desmet, V., 79-6094
Desrosiers, R. C., 79-6425
Dev, V. G., 79-6449
Devens, B., 79-6486
Dezhbakhsh, F., 79-6589
Diaz-Flores, L., 79-6535
Diel, J. H., 79-6372
Dietz, M., 79-6408
Dina, D., 79-6413

- DiVito, N., 79-6139
 Dock, N. L., 79-6482
 Dockerty, M. B., 79-6217
 Doll, R., 79-6022
 Domae, N., 79-6481
 Domellof, L., 79-6512
 Domoradzki, J., 79-6430
 Donham, K. J., 79-6231
 Donner, M., 79-6248
 Douglas, G. R., 79-6264
 Drahovsky, D., 79-6156, 79-6594
 Drinkwater, N. R., 79-6246
 Drummond, M., 79-6037
 Dublin, N., 79-6587
 Dudley, J. P., 79-6395
 Duffy, D. M., 79-6370
 Dufour, M., 79-6330
 Dunkel, V. C., 79-6242
 Dunn, D. L., 79-6244
 Duris, I., 79-6218
 Dusheiko, G. M., 79-6506
 Dux, A., 79-6405
 Dybing, E., 79-6167, 79-6235
 Dziubko, N. Ia., 79-6311
 Eadie, T., 79-6281
 Eakins, K. E., 79-6272
 East, J., 79-6366
 Edwards, C. A., 79-6447
 Edwards, G. S., 79-6182
 Ehling, U. H., 79-6239
 Ehmann, U. K., 79-6357
 Ehrenberg, L., 79-6049
 Ehrich, M., 79-6575
 El Etreby, M. F., 79-6350
 79-6352
 El Sheikh, E. H., 79-6554
 Elequin, F., 79-6466
 Elespuru, R. K., 79-6212
 Elias, L., 79-6579
 Elkind, M. M., 79-6360
 Elston, R. C., 79-6540
 Emami, H., 79-6280
 Endo, A., 79-6135
 English, M., 79-6440
 Enriquez, R. E., 79-6487
 Epler, J. L., 79-6130
 Epstein, M. A., 79-6428
 Erikson, E., 79-6382
 Erikson, R. L., 79-6382
 79-6386
 Erkulrawatr, S., 79-6528
 Essex, M., 79-6292
 Estrada, R., 79-6368
 Evans, J. M., 79-6097
 Evans, V. J., 79-6129
 Evsejenko, L. S., 79-6536
 Faed, M., 79-6359
 Fajen, J. M., 79-6182
 Fan, T. Y., 79-6182
 Faras, A. J., 79-6386
 Farber, E., 79-6063
 Fareed, G. C., 79-6442
 Farrell, R. E., 79-6547
 Farrelly, J. G., 79-6212
 Farrer, K. T., 79-6042
 Faulkin, L. J., 79-6396
 Fazzini, E., 79-6208
 Fechner, R. E., 79-6368
 Fedosov, E. A., 79-6485
 Fedrich, J., 79-6558
 Feldman, J. M., 79-6547
 Felkner, I. C., 79-6174
 Fenyo, E. M., 79-6077
 Ferrini, U., 79-6192
 Festenstein, H., 79-6477
 Feunteun, J., 79-6417
 Fialkow, P. J., 79-6306
 Fine, D. H., 79-6182
 Finerty, S., 79-6428
 Fischer, G., 79-6516
 Fisher, P. B., 79-6268
 Fitzgerald, P. J., 79-6508
 Fitzpatrick, T. B., 79-6071
 Fleckenstein, B., 79-6425
 Flink, E., 79-6116
 Flood, M. K., 79-6381
 Floot, B. G., 79-6184
 Fluck, M. M., 79-6438
 Fogh, J., 79-6508
 Fomina, M. M., 79-6536
 Fouchey, S., 79-6408
 Francia Vina, J. M., 79-6111
 Francke, U., 79-6422
 Frank, C. W., 79-6231
 Frank, N., 79-6148
 Fraser, P., 79-6560
 Fredlund, P. E., 79-6176
 Freedman, H. J., 79-6296, 79-6313
 Fridman-Manduzio, A., 79-6193
 Friedrich, R., 79-6379
 Fukuda, M., 79-6596
 Fukuda, T., 79-6223
 Fukuhara, H., 79-6152
 Furmanski, P., 79-6408
 Furstemberger, G., 79-6275
 Furukawa, K., 79-6171
 Gadaginamath, G., 79-6017
 Gaede, J. T., 79-6547
 Gagliardi, F. M., 79-6529
 Gak, J. C., 79-6343, 79-6344
 Gal, D., 79-6552
 Galegov, G. A., 79-6402
 Galili, N., 79-6486
 Galton, J. E., 79-6363
 Gammal, T. E., 79-6528
 Gantt, R. R., 79-6129
 Gardner, M. B., 79-6412
 Garner, R. C., 79-6206
 Garon, C. F., 79-6410
 Gaskill, S. P., 79-6571
 Gasparini, M., 79-6562
 Gasparotto, G., 79-6511
 Gaugler, B. J., 79-6340
 Gazdar, A. F., 79-6422
 Gazit, A., 79-6461
 Gear, A. J., 79-6506
 Gebel, H. M., 79-6489
 Geboes, K., 79-6094
 Gentil, A., 79-6309
 Gerwin, B. I., 79-6416
 Getaz, E. P., 79-6369
 Ghassemi, H., 79-6589
 Giacherio, D., 79-6441
 Gianni, C., 79-6562
 Gibinski, K., 79-6561
 Gibson, D. D., 79-6301
 Gilbert, E. S., 79-6576
 Gillette, J. R., 79-6008
 Gillis, A. E., 79-6407
 Gillis, S., 79-6407
 Giner-Sorolla, A., 79-6232
 Gingell, R., 79-6196
 Girard, M., 79-6446
 Gissmann, L., 79-6420
 Glatt, H. R., 79-6316, 79-6341
 Glaumann, H., 79-6167
 Glebatis, D., 79-6116
 Glover, E., 79-6250
 Gloxhuber, C., 79-6018
 Go, R. C., 79-6540
 Godal, A., 79-6330
 Goeken, J. A., 79-6473
 Goff, U. E., 79-6182
 Golan, M., 79-6316
 Golberg, L., 79-6043
 Goldstein, D. A., 79-6440
 Gondos, B., 79-6499
 Good, R. A., 79-6470
 Goodman, D. G., 79-6541
 Goodman, J. I., 79-6168
 Gotoh, M., 79-6171
 Gotohda, E., 79-6509
 Gottlieb, A. J., 79-6482
 Gotto, A. M., 79-6247
 Graessmann, A., 79-6443
 Graessmann, M., 79-6443
 Graf, K. J., 79-6350, 79-6352
 Graham, S., 79-6114
 Grailott, C., 79-6343, 79-6344
 Grant, C. E., 79-6264
 Grassi, A., 79-6563
 Grauman, D., 79-6580
 Green, C., 79-6406
 Green, J. B., 79-6528
 Green, M., 79-6451, 79-6454
 Green, S., 79-6213
 Greenbaum, J. H., 79-6232
 Greenfield, R., 79-6076
 Greenspan, J. R., 79-6574
 Griffin, B. E., 79-6433
 Griffith, O. H., 79-6317
 Griffiths, T. D., 79-6362
 Gross, L., 79-6072
 Grosser, P. J., 79-6126
 Grover, P. L., 79-6014, 79-6289
 79-6293, 79-6309, 79-6312
 79-6333
 Grubbs, C. J., 79-6290
 Grunberger, D., 79-6335
 Grynevych, Iu. A., 79-6311
 Guerin, M. R., 79-6130
 Guirgis, H. A., 79-6540
 Gundy, S., 79-6354
 Gurevitch, A. W., 79-6370
 Gurtoo, H. L., 79-6296, 79-6313
 Gutman, E., 79-6587
 Haas, M., 79-6399
 Haegle, K. D., 79-6254
 Haenisch, F., 79-6341
 Haenszel, W., 79-6114
 Hager, G. L., 79-6410
 Hager, L. P., 79-6441
 Hagerstrand, I., 79-6542
 Haghighi, P., 79-6589
 Haglund, U., 79-6145
 Hagopian, M., 79-6262
 Haidak, D. J., 79-6133
 Hainau, B., 79-6203
 Hakanson, R., 79-6539
 Hakomori, S., 79-6596
 Hakura, A., 79-6435
 Halbert, D. N., 79-6456
 Haldemann, R., 79-6124
 Haley, T. J., 79-6050
 Hall, J. D., 79-6356
 Hall, L., 79-6408
 Hammond, E. C., 79-6052
 Han, A., 79-6360
 Han, T., 79-6475
 Hancock, R. L., 79-6030
 Handleman, S. L., 79-6129
 Hansen, N. E., 79-6524
 Hansz, J., 79-6592
 Harada, H., 79-6302
 Haraguchi, S., 79-6498
 Harrington, G. W., 79-6245
 Harris, C. C., 79-6315
 Harris, R. E., 79-6540
 Harrison, P. V., 79-6520
 Hart, A. A., 79-6184
 Harter, M. L., 79-6452
 Hartman, S. P., 79-6149
 Harvey, J. J., 79-6366
 Harvey, R. G., 79-6336
 Haseltine, W. A., 79-6423
 Haskill, S., 79-6517, 79-6518
 Hauser, G. A., 79-6122
 Hawkins, J., 79-6528
 Hayakawa, T., 79-6459
 Hayata, I., 79-6367
 Hecht, S. S., 79-6305
 Hecker, E., 79-6189
 Hecker, L. I., 79-6212
 Hellman, K. B., 79-6392
 Hemalatha, V., 79-6555
 Henderson, B. E., 79-6573
 Henderson, P. T., 79-6323
 Henschler, D., 79-6151
 Henson, P., 79-6377
 Herrmann, E. C., 79-6128
 Hershey, E. J., 79-6401
 Hesbert, A., 79-6169
 Heude, M., 79-6152
 Hewer, A., 79-6289, 79-6333
 Hilgers, J., 79-6398, 79-6405
 Hill, A. P., 79-6574
 Hill, M. J., 79-6101
 Hillman, E., 79-6315
 Hilton, P., 79-6504
 Hirai, K., 79-6257
 Hirai, R., 79-6414
 Hirakawa, T., 79-6328
 Hirano, T., 79-6470
 Hirashima, K., 79-6367
 Hirose, F. M., 79-6370
 Hirota, N., 79-6305
 Hirschman, S. Z., 79-6080
 Hites, R. A., 79-6326
 Hobbs, M. S., 79-6585
 Hochwald, G. M., 79-6363
 Hoehn, S. K., 79-6300
 Hoel, D., 79-6032
 Hoerner, H. E., 79-6527
 Hoff, M. B., 79-6116
 Hoffken, K., 79-6507
 Hoffman, E. M., 79-6488
 Hoffman, K. M., 79-6174
 Hoffmann, D., 79-6241, 79-6305
 79-6420
 Holland, J. F., 79-6476
 Holliday, R., 79-6103
 Hollstein, M., 79-6048
 Holmes, H. C., 79-6366
 Holmquist, N. D., 79-6426
 Holtzer, H., 79-6271
 Holtzman, S., 79-6299
 Homburger, F., 79-6044, 79-6284
 Hoon, B. S., 79-6385
 Hooper, N. K., 79-6002
 Hoover, E. A., 79-6419
 Hoover, R. G., 79-6489
 Hopkins, D., 79-6416
 Hopper, K. E., 79-6495
 Hori, M., 79-6459
 Horkay, I., 79-6354
 Horning, E. C., 79-6007
 Horvath, E., 79-6502
 Houle, W. A., 79-6317
 Hourihan, S. L., 79-6439
 Houston, K. J., 79-6448
 Howatson, A. F., 79-6090
 Hradec, J., 79-6338
 Hu, S. S., 79-6384
 Huang, L., 79-6197
 Huchhausen, B., 79-6420
 Huebner, K., 79-6406
 Hughes, J., 79-6570
 Hultin, T., 79-6185
 Hunter, N., 79-6493
 Huntington, H. W., 79-6530
 Hwang, K. K., 79-6162
 Ianculescu, M., 79-6461
 Ichinose, H., 79-6527
 Ikeda, M., 79-6564
 Imai, S., 79-6398
 Inui, N., 79-6180
 Ishak, K. G., 79-6574
 Ishihara, T., 79-6367
 Israel, M. A., 79-6410, 79-6434
 79-6439
 Ito, N., 79-6188
 Ito, Y., 79-6479
 Iyer, R. P., 79-6327
 Izaguirre, C. A., 79-6090
 Izmerov, N. F., 79-6108
 Izu, M., 79-6347
 Jabara, A. G., 79-6345
 Jacobs, T. P., 79-6533
 Jacobson, R. J., 79-6133
 Jacquignon, P., 79-6330
 Jain, D. K., 79-6583
 Jakubovsky, J., 79-6218
 Jalanko, H., 79-6234
 James, W. P., 79-6559
 Jande, S. S., 79-6307
 Janerich, D. T., 79-6116
 Janunger, K. G., 79-6512
 Jaspers, N. G., 79-6355

Jay, G., 79-6383
 Jeffrey, A. M., 79-6315
 Jensen, D. M., 79-6565
 Jensen, M. K., 79-6524
 Jerina, D. M., 79-6015, 79-6017
 79-6304, 79-6308, 79-6334
 Ji, C., 79-6197
 Joel-Cohen, S. J., 79-6567
 Johansson-Brittebo, E., 79-6183
 Jones, P. P., 79-6472
 Jose, D., 79-6041
 Joyner, C. A., 79-6577
 Jukes, T. H., 79-6047
 Jussawalla, D. J., 79-6583
 Kabat, E. A., 79-6490
 Kaden, D. A., 79-6326
 Kadish, A., 79-6466
 Kadlubar, F. F., 79-6246
 Kafka, I., 79-6476
 Kagan, E., 79-6133
 Kahan, B. D., 79-6087
 Kalmykova, Z. I., 79-6373
 79-6375
 Kanai, N., 79-6459
 Kane, L. N., 79-6346
 Kanter, P. M., 79-6591
 Kaplan, E., 79-6540
 Karki, N. T., 79-6322
 Karle, J. M., 79-6017, 79-6304
 Kashmiri, S. V., 79-6416
 Katsuta, H., 79-6195
 Katyal, S. L., 79-6194
 Kaufman, D. G., 79-6325
 Kawashima, K., 79-6479
 Keck, K., 79-6437
 Kedar, E., 79-6476
 Keijzer, W., 79-6355
 Keller, P., 79-6255
 Keller, R., 79-6497
 Kelley, D. S., 79-6598
 Kelsey, J. L., 79-6117
 Kelsey, M. I., 79-6162
 Kennedy, A. R., 79-6361
 Kennel, S. J., 79-6460
 Kerler, R., 79-6186
 Kerr, A., 79-6230
 Kertai, P., 79-6187
 Keski-Oja, J., 79-6267
 Kew, M. C., 79-6506
 Khoury, G., 79-6450
 Kikugawa, K., 79-6179
 Kimbrough, R. D., 79-6005
 Kimura, M., 79-6223
 King, C. M., 79-6173
 King, D. T., 79-6370
 King, M. M., 79-6301, 79-6516
 Kinmont, P. D., 79-6355
 Kirkpatrick, C. H., 79-6501
 Kishimoto, T., 79-6470
 Kissomergis, A. M., 79-6303
 Kitamura, H., 79-6459
 Klaassen, C. D., 79-6147
 Kleihues, P., 79-6065
 Klein, E., 79-6486
 Klein, G., 79-6078
 Kleinhofs, A., 79-6144
 Klimek, R., 79-6096
 Klippel, J. H., 79-6580
 Knapp, M. R., 79-6469, 79-6471
 79-6472
 Knauer, D. J., 79-6387
 Kneist, S., 79-6256
 Koene, R. A., 79-6496
 Kollmorgen, G. M., 79-6516
 Koltin, Y., 79-6261
 Kono, S., 79-6564
 Korobowicz, E., 79-6523
 Koropatnick, D. J., 79-6137
 Koruda, M., 79-6282
 Kouri, R. E., 79-6318
 Koutecky, J., 79-6510
 Kovacs, K., 79-6502
 Kowbel, D. J., 79-6264
 Koyama, K., 79-6596
 Kozlov, Iu. P., 79-6465

Krawiec, J., 79-6566
 Krech, R., 79-6215
 Kress, M., 79-6446
 Kreutner, A., 79-6577
 Krieger, G., 79-6255
 Kritchevsky, D., 79-6204
 Krueger, R. G., 79-6504
 Krupa, T. A., 79-6270
 Krzyzek, R. A., 79-6386
 Kuhnlein, U., 79-6140
 Kula, N., 79-6279
 Kulkarni, P., 79-6272
 Kumar, M. S., 79-6595
 Kumazawa, T., 79-6302
 Kunze, M., 79-6584
 Kurechi, T., 79-6179
 Kuritani, T., 79-6470
 Kurland, L. T., 79-6217
 Kusumoto, T., 79-6302
 Kute, T. E., 79-6346
 Kvicala, J., 79-6338
 La Bella, F., 79-6600
 Lai, C. N., 79-6131
 Lai, M., 79-6415
 Lai, M. M., 79-6384
 Lake, J., 79-6390
 Lamb, J. C., 79-6342
 Lancet, C., 79-6344
 Lanford, R. E., 79-6445
 Lankin, V. Z., 79-6536
 Larsen, S. H., 79-6391
 Last-Barney, K., 79-6232
 Latt, S. A., 79-6273
 Lau, A. F., 79-6386
 Lavery, R., 79-6324
 LaVoie, E., 79-6305
 Lawson, T., 79-6196
 Lawther, P. J., 79-6105
 Le Mesurier, S. M., 79-6207
 Leavitt, J., 79-6599
 Lee, I. S., 79-6578
 Lee, J. S., 79-6380
 Lee, P. W., 79-6464
 Legator, M. S., 79-6023
 Legrue, S. J., 79-6087
 Lehman, A. A., 79-6516
 Lehr, R. E., 79-6015
 Lemonnier, M., 79-6169
 Lemons, R. S., 79-6421
 Leroy-Houyet, M. A., 79-6229
 LeSturgeon, D. N., 79-6385
 Levin, J. G., 79-6416
 Levin, W., 79-6015, 79-6017
 79-6304, 79-6308, 79-6334
 Levine, A. J., 79-6075, 79-6450
 Levine, A. S., 79-6432
 Levis, A. G., 79-6136
 Levitt, D. S., 79-6167
 Levitt, L. J., 79-6585
 Levitt, R. C., 79-6318
 Levy, S., 79-6321
 Lewis, A. M., 79-6458, 79-6501
 Lewis, J. B., 79-6452
 Lewko, W. M., 79-6346
 Li, M. H., 79-6197
 Liebeskind, D., 79-6466
 Lieveaux, A., 79-6551
 Liggins, G. L., 79-6440
 Lijinsky, W., 79-6202
 Lin, J. K., 79-6237
 Linden, W. A., 79-6590
 Lindgren, J., 79-6512
 Linhart, M. S., 79-6541
 Linz, U., 79-6420
 Little, J. B., 79-6361, 79-6377
 Litvay, M., 79-6031
 Llewellyn, G. C., 79-6281
 Lombardi, B., 79-6194
 Lombardi, F., 79-6562
 Long, C., 79-6393
 Longley, R. E., 79-6516
 Lortz, Z. M., 79-6173
 Losikoff, A. M., 79-6263
 Louie, E. W., 79-6573
 Loveday, K. S., 79-6273

Lovett, D. H., 79-6487
 Lowy, D. R., 79-6410
 Lu, S. H., 79-6197
 Lubet, R. A., 79-6244
 Lundberg, K., 79-6390
 Lutz, M. H., 79-6577
 Lutz, W. K., 79-6021
 Lykke, A. W., 79-6207
 Lynch, H. T., 79-6540
 Lynch, J. F., 79-6540
 Lynch, P. M., 79-6540
 Lynch, R. G., 79-6489
 Lyon, J. L., 79-6114
 Mach, B., 79-6491
 MacKinnon, E. A., 79-6224
 MacLennan, R., 79-6051
 MacLeod, M. C., 79-6332
 Macnicoll, A. D., 79-6289
 Macrae, W. D., 79-6138, 79-6224
 Maddock, C., 79-6433
 Magee, P. N., 79-6064
 Magrath, I. T., 79-6432
 Mah, H. D., 79-6017, 79-6304
 79-6334
 Maier, G., 79-6506
 Majone, F., 79-6136
 Majsky, A., 79-6510
 Malaveille, C., 79-6165
 79-6293
 Malenica, B., 79-6161
 Malik, M. O., 79-6554
 Mallik, H. V., 79-6243
 Mann, D. L., 79-6084
 Manz, H. J., 79-6532
 Marchok, A. C., 79-6220
 Margolskee, R. F., 79-6391
 Marinello, A. J., 79-6313
 Markovits, P., 79-6320, 79-6321
 Marks, F., 79-6275
 Marks, G. N., 79-6345
 Marks, S., 79-6576
 Marks, S. M., 79-6480
 Martin, C. N., 79-6206
 Martin, M. A., 79-6410, 79-6434
 79-6439
 Martin, R. G., 79-6447
 Mass, M. J., 79-6325
 Massey, R., 79-6393
 Mastro, A. M., 79-6270
 Mathes, L. E., 79-6419
 Matney, T. S., 79-6254
 Matsuda, Y., 79-6429
 Matsumoto, H., 79-6146
 Matsumoto, K., 79-6347, 79-6349
 Matsumoto, M., 79-6201
 Matsuo, T., 79-6498
 Matsushima, T., 79-6146
 Mattei, E., 79-6192
 Mattison, D. R., 79-6314
 Mattula, T. I., 79-6264
 Maunoury, R., 79-6321
 Mavligit, G. M., 79-6505
 Mayer, D., 79-6215
 Mazur, E. M., 79-6487
 Mazzares, R., 79-6305
 Mc Coy, E. C., 79-6178
 McCann, J., 79-6048
 McCay, P. B., 79-6301, 79-6516
 McConnell, R. B., 79-6100
 McCormick, K. J., 79-6079
 McCulloch, E. A., 79-6090
 McCullough, D. C., 79-6532
 McDonald, H. M., 79-6519
 McFee, A. F., 79-6225
 McGuire, W. L., 79-6571
 McLachlan, J. A., 79-6342
 McMichael, A. J., 79-6586
 McNulty, J. C., 79-6585
 Meek, E. S., 79-6231
 Mehta, R., 79-6331
 Meites, J., 79-6027
 Melissinos, K., 79-6543
 Mellstedt, H., 79-6503
 Mendez, F., 79-6466
 Meredith-Brown, M., 79-6331

Meshorer, A., 79-6399
 Messripour, M., 79-6280
 Metakis, L. J., 79-6500
 Metera, M., 79-6523
 Metzler, M., 79-6024, 79-6341
 Michelsen, J., 79-6533
 Mikuni-Takagaki, Y., 79-6389
 Milas, L., 79-6161
 Miller, E. C., 79-6020, 79-6246
 Miller, H. J., 79-6112
 Miller, J. A., 79-6020, 79-6246
 Miller, M. C., 79-6577
 Miller, P., 79-6590
 Minden, M. D., 79-6090
 Minenkova, E. A., 79-6536
 Minna, J. D., 79-6422
 Minowada, J., 79-6296, 79-6313
 79-6475
 Mirmomeni, M. H., 79-6280
 Mirvish, S. S., 79-6214
 Missier, P., 79-6537
 Mitchell, J. R., 79-6007
 Mitchell, R. L., 79-6418
 Mitchell, R. S., 79-6385
 Mittler, S., 79-6364
 Miyamoto, H., 79-6498
 Miyata, Y., 79-6188
 Moake, J. L., 79-6505
 Mochizuki, Y., 79-6171
 Moelling, K., 79-6379
 Mohammad, A. R., 79-6298
 Mohr, S. J., 79-6478
 Mojtabai, A., 79-6563
 Moldow, C. F., 79-6390
 Molina, J. E., 79-6162
 Moloney, W. C., 79-6480
 Money-Kyrle, A. F., 79-6019
 Monjardino, J., 79-6462
 Monson, R., 79-6262
 Montie, J. E., 79-6085
 Moon, R. C., 79-6200
 Moore, C. W., 79-6252
 Moore, F. B., 79-6238
 Moore, V. E., 79-6310
 Morgan, R. W., 79-6071
 Morgan, W. F., 79-6353
 Morgenroth, V. H., 79-6061
 Mori, M., 79-6180
 Mori, T., 79-6188
 Morii, S., 79-6302
 Morris, J. A., 79-6526
 Morrisett, J. D., 79-6247
 Morrissey, P. J., 79-6083
 Morton, S. G., 79-6281
 Mostafavi, N., 79-6589
 Mourelatos, D., 79-6359
 Moustacchi, E., 79-6152
 79-6357
 Mueller, C., 79-6443
 Mueller-Lantzsch, N., 79-6431
 Mufson, R. A., 79-6268, 79-6272
 79-6277, 79-6278
 Muir, C. S., 79-6557
 Mulder, C., 79-6425
 Munoz, N., 79-6563
 Munro, I. C., 79-6045
 Muraguchi, A., 79-6470
 Murphy, P. J., 79-6230
 Murray, C., 79-6084
 Murthy, A. S., 79-6262
 Murthy, M. S., 79-6286
 Musumeci, R., 79-6562
 Nabizadeh, I., 79-6589
 Nachnani, G. H., 79-6133
 Nagarajan, B., 79-6236
 Nagasawa, H., 79-6361
 Nagel, D., 79-6196
 Nagy, E., 79-6354
 Nakagawa, H., 79-6459
 Nakamura, I., 79-6468
 Nakanishi, K., 79-6188
 Nakata, Y., 79-6459
 Nakayama, E., 79-6483
 Nakopoulou, L., 79-6543
 Naor, D., 79-6486

- Nasim, A., 79-6013
Natarajan, A. T., 79-6205
79-6209
Nathans, D., 79-6391
Nebert, D. W., 79-6318
Neeser, E., 79-6120
Nelson, D. S., 79-6495
Nelson, N., 79-6113
Nelson-Rees, W. A., 79-6292
79-6424
Nelson, S. D., 79-6007
Nemoto, N., 79-6328
Nestmann, E. R., 79-6264
Nettesheim, P., 79-6220
79-6276
Neubauer, R. H., 79-6424
Neuhoff, S., 79-6552
Neumann, F., 79-6352
Neumann, H. G., 79-6024
79-6340
Nevasaari, K., 79-6322
Newberne, P. M., 79-6279
Newbold, R. F., 79-6336
Newbold, R. R., 79-6342
Newburg, D. S., 79-6258
Nicolini, C., 79-6590
Nicolov, I. G., 79-6285
Nicolson, G. L., 79-6534
79-6593
Nilan, R. A., 79-6144
Ninfo, V., 79-6511
Nishi, Y., 79-6180
Nishiyama, Y., 79-6427
Niyogi, S. K., 79-6444
Noller, K. L., 79-6217
Nomura, T., 79-6198
Nomura, Y., 79-6347, 79-6349
Nonoyama, M., 79-6424
Noronha-Blob, L., 79-6265
Novikovs, L., 79-6432
Nowak, A., 79-6561
Nudelman, E., 79-6596
Nye, J. S., 79-6499
Nygard, O., 79-6185
O'Brien, S. J., 79-6421
O'Connor, P. J., 79-6170
O'Fallon, W. M., 79-6217
O'Neill, B. J., 79-6416
Ochi, H., 79-6347
Odes, H. S., 79-6566
Oesch, F., 79-6316, 79-6329
79-6341
Oettgen, H. F., 79-6483
Ohmori, T., 79-6305
Oie, H., 79-6422
Oikawa, T., 79-6509
Okada, Y. S., 79-6435
Okamoto, R., 79-6347
Okuno-Kaneda, S., 79-6166
Old, L. J., 79-6483
Olsen, R. G., 79-6419
Opferkuch, H. J., 79-6189
Oppenheim, B. E., 79-6069
Ory, H. W., 79-6574
Osborne, C. K., 79-6571
Osborne, M. R., 79-6283
Oskarsson, A., 79-6142
Oste, R., 79-6176
Owais, W. M., 79-6144
Pai, K. J., 79-6284
Paigen, B., 79-6296
Palladino, M. A., 79-6363
Pallesen, G., 79-6524
Papac, R. J., 79-6487
Papacharalampous, N., 79-6543
Papadopoulos, D., 79-6320
79-6321
Park, D. C., 79-6346
Parker, N. B., 79-6313
Parker, V. H., 79-6134
Parkes, H. G., 79-6011
Parkinson, D. R., 79-6083
Parrish, J. A., 79-6071
Parshad, R., 79-6129
Parthenais, E., 79-6517
79-6518
Pastan, I. H., 79-6383
Pasternak, G., 79-6086
Paterson, M. E., 79-6348
Patrianakos, C., 79-6241
Paulus, H., 79-6143
Payette, R., 79-6030
Pelkonen, O., 79-6318, 79-6322
Penn, I., 79-6009
Pequignot, G., 79-6565
Peracchia, A., 79-6511
Perk, K., 79-6461
Peters, F. D., 79-6120
Peters, L. J., 79-6493
Petrillo, R., 79-6562
Petrullo, L. A., 79-6178
Pettersson, D., 79-6503
Pettinelli, C. B., 79-6082
Pfaffenroth, M. J., 79-6210
Pfister, H., 79-6420
Pfleiderer, A., 79-6118
Phelps, M., 79-6430
Philip, P., 79-6524
Philippus, E. J., 79-6184
Phillips, T. M., 79-6532
Pickering, C., 79-6206
Pienta, R. J., 79-6288
Pike, M. C., 79-6573
Pinter, A., 79-6057
Pitha, J., 79-6265
Pitha, J. V., 79-6301
Pitot, H. C., 79-6246
Pizzo, P. A., 79-6432
Piaat, D., 79-6457
Pliss, G. B., 79-6251
Plotz, P. H., 79-6580
Podany, V., 79-6330
Pogrel, M. A., 79-6531
Pooley, J. A., 79-6288
Poland, A., 79-6250
Polani, P. E., 79-6092
Polay, J. S., 79-6533
Polimeni, P. I., 79-6385
Politano, V. A., 79-6095
Polley, M. J., 79-6500
Popperova, E., 79-6218
Poroshenko, G. G., 79-6536
Poste, G., 79-6381, 79-6593
Potter, V. R., 79-6598
Poulsen, E., 79-6110
Pour, P., 79-6196, 79-6508
79-6544
Powell, L., 79-6527
Pozharisski, K. M., 79-6175
Pradalier, A., 79-6093
Prat, M., 79-6388
Pravdina, N. F., 79-6402
Preissig, S. H., 79-6376
79-6530
Pretell, J., 79-6076
Price, F. M., 79-6129
Price, M. R., 79-6039, 79-6310
79-6507
Prough, R. A., 79-6244
Prunieras, M., 79-6062
Pullman, B., 79-6324
Purchio, A. F., 79-6382
Quintart, J., 79-6229
Qureshi, S. A., 79-6154
Raanan, Z., 79-6476
Rabes, H. M., 79-6186
Rabin, H., 79-6424
Radhakrishnan, S., 79-6582
Radl, J., 79-6467
Rady, P., 79-6187
Raicht, R. F., 79-6208
Raineri, R., 79-6288
Rajalakshmi, S., 79-6063
Ralph, P., 79-6470
Rao, P. M., 79-6063
Rao, T. K., 79-6130
Rao, U., 79-6369
Rapp, F., 79-6427
Rasanen, O., 79-6297
Rasheed, S., 79-6412
Raskas, H. J., 79-6456
Rastogi, R. B., 79-6307
Ray, J. H., 79-6238
Ray, V., 79-6004
Reddy, A. L., 79-6306
Reddy, B. S., 79-6204
Reddy, J. K., 79-6154
Rees, R. C., 79-6039
Reese, D. H., 79-6095
Reichel, G. W., 79-6376
Rein, A., 79-6416
Reinhold, V., 79-6182
Reintoft, I., 79-6542
Renwick, A. G., 79-6253
Repanti, M., 79-6543
Reske-Kunz, A. B., 79-6500
Reuber, M. D., 79-6003, 79-6240
79-6259
Reynolds, F. H., 79-6390
Rhim, J. S., 79-6292
Ribeiro, O., 79-6289, 79-6333
Rich, M. A., 79-6408
Richardson, N. J., 79-6575
Richert, N. D., 79-6383
Rickwood, A. M., 79-6555
Riess, H., 79-6186
Rinkus, S. J., 79-6023
Ritper, D. L., 79-6010
Robert, N., 79-6083
Roberts, W. P., 79-6230
Robey, W. G., 79-6400
Robinson, H. L., 79-6074
Rode, G., 79-6186
Roemer, V. M., 79-6120
Roger, M., 79-6093
Roggli, V. L., 79-6368
Rojko, J. L., 79-6419
Roman, A., 79-6436
Rooks, J. B., 79-6574
Rosen, J. D., 79-6056
Rosenberg, N., 79-6403
Rosenkranz, H. S., 79-6178
Rosenthal, D. S., 79-6480
Ross, R. K., 79-6573
Rothstein, M., 79-6245
Rounbehler, D. P., 79-6182
Rowe, W. P., 79-6434, 79-6439
Rowell, N. R., 79-6520
Roy-Burman, P., 79-6415
Roy, S., 79-6573
Rubinstein, A., 79-6466
Rudiger, H. W., 79-6341
Ruhland, A., 79-6191
Ruiz, P., 79-6488
Ruoslathi, E., 79-6234
Rupniewska, Z. M., 79-6523
Ruscetti, S. K., 79-6407
Russfield, A. B., 79-6262
Rustia, M., 79-6216
Rutt, G., 79-6580
Rutzky, L. P., 79-6087
Ryan, D. E., 79-6304
Ryan, K. J., 79-6351
Ryan, W., 79-6295
Rybicka, J., 79-6561
Rydstrom, P. O., 79-6155
Sabadie, N., 79-6165
Sabine, J. R., 79-6026
Sacks, T. L., 79-6401
Sadeghi, A., 79-6581
Sado, T., 79-6367
Sahagan, B. G., 79-6423
Sakamoto, A., 79-6349
Sakamoto, G., 79-6349
Sakamoto, Y., 79-6459
Saleh, M. A., 79-6002
Salmasi, S., 79-6196
Salmasi, S. Z., 79-6544
Salmassi, S., 79-6589
Salmi, T., 79-6568
Sandberg, A. A., 79-6226
79-6522
Sanders, S. M., 79-6374
Sanford, K. K., 79-6129
Sankaranarayanan, N., 79-6286
Sanotski, I. V., 79-6108
Sansing, W. A., 79-6516
Sansone, E. B., 79-6263
Santamaria, L., 79-6287
Santella, R. M., 79-6335
Santillana, M., 79-6409
Sardella, D. J., 79-6282
Sarma, D. S., 79-6063
Sarraf, A. M., 79-6139
Sarwal, A. N., 79-6208
Sasame, H. A., 79-6219
Sato, K., 79-6223
Satoh, M., 79-6459
Sawada, H., 79-6481
Sawamura, M., 79-6146
Scharf, A. M., 79-6139
Schafer, P. W., 79-6315
Schaller, J. P., 79-6419
Scheid, M. P., 79-6500
Scherneck, S., 79-6417
Schirmeister, J., 79-6255
Schirrmacher, V., 79-6484
Schlossman, S. F., 79-6480
Schmahl, D., 79-6058, 79-6211
Schmassmann, H. U., 79-6316
Schmick, A., 79-6252
Schmidt, R., 79-6189
Schmidt, W., 79-6477
Schmitt-Verhulst, A. M.
79-6082
Schochetman, G., 79-6393
Schoental, R., 79-6098
Schollmeyer, J., 79-6386
Schroder, J., 79-6471
Schupbach, M. E., 79-6228
Schuphan, I., 79-6056
Schwartz, E. L., 79-6168
Schwartz, H. S., 79-6591
Schwartz, R. A., 79-6132
Scolnick, E. M., 79-6407
79-6410, 79-6411, 79-6415
Scornik, J. C., 79-6488
Sebastian, H., 79-6538
Segal, A., 79-6567
Segal, S., 79-6450
Sehon, A. H., 79-6502
Sekiya, S., 79-6028
Selikoff, I. J., 79-6052
Selkirk, J. K., 79-6327
79-6332
Sell, S., 79-6038, 79-6172
79-6194
Sells, M. A., 79-6194
Selsky, C. A., 79-6377
Seltzer, V., 79-6587
Semenzato, G., 79-6511
Sen, A., 79-6400
Seno, T., 79-6166
Setlow, R., 79-6067
Setlow, V. P., 79-6447
Severinson-Gronowicz, E.
79-6471
Shah, H., 79-6149
Shantz, G., 79-6484
Shapiro, S., 79-6025
Shapov, V. S., 79-6001
Sharkey, F. E., 79-6508
Sharp, P. A., 79-6453
Shaw, C. R., 79-6254
Shaw, S., 79-6082
Shearer, G. M., 79-6082
Shelburne, J. D., 79-6547
Shellabarger, C. J., 79-6299
Shergalis, W. A., 79-6245
Sherr, C. J., 79-6421
Sherrill, M. N., 79-6225
Shestakova, S. V., 79-6465
Sheu, C. J., 79-6213
Shevlyagin, V. Y., 79-6073
Shih, T. Y., 79-6411, 79-6415
Shikata, N., 79-6302
Shiku, H., 79-6483
Shimada, T., 79-6135
Shimaoka, K., 79-6369
Shinozuka, H., 79-6194

Shirai, A., 79-6146
 Shiraiishi, Y., 79-6226
 Shirakawa, S., 79-6481
 Short, R. K., 79-6372
 Shoyab, M., 79-6267, 79-6291
 79-6294
 Shubik, P., 79-6216
 Simmons, D. T., 79-6439
 Simpson, M., 79-6404
 Sims, P., 79-6014, 79-6289
 79-6293, 79-6309, 79-6312
 79-6333
 Singhal, R. L., 79-6307
 Sipponen, P., 79-6512
 Sitkovskii, M. V., 79-6465
 Sivak, A., 79-6036
 Skinnider, L. F., 79-6269
 Skolnik, H., 79-6442
 Slaga, T. J., 79-6327
 Slavin, S., 79-6469, 79-6472
 Slone, D., 79-6025
 Smart, C. E., 79-6238
 Smart, V. B., 79-6337
 Smith, G. L., 79-6387
 Smith, J. W., 79-6426
 Smith, K. A., 79-6407
 Smith, L. L., 79-6337
 Smith, M. T., 79-6376, 79-6530
 Smith, P., 79-6270
 Smoliar, V., 79-6193
 Snell, J., 79-6262
 Snoek, M., 79-6514
 Solter, D., 79-6089
 Somers, E., 79-6107
 Sommers, S. C., 79-6537
 Soprano, K. J., 79-6449
 Sorg, B., 79-6189
 Sorsa, M., 79-6248
 Soto, E., 79-6284
 Southwick, G. J., 79-6132
 Spallone, A., 79-6529
 Spechter, H. J., 79-6119
 Spector, D. J., 79-6456
 Spellman, C. W., 79-6071
 Squire, R. A., 79-6541
 Srinivasan, G., 79-6528
 St. George, J. A., 79-6396
 Stamberg, J., 79-6261
 Stibolis, C., 79-6545, 79-6546
 Stasiacki, P., 79-6316
 Staszewski, J., 79-6557
 Steele, V. E., 79-6220
 Stein, B. S., 79-6538
 Steinmetz, M., 79-6491
 Stenback, F., 79-6295
 Stepan, K., 79-6544
 Stepanova, L. G., 79-6227
 Stephenson, J. R., 79-6390
 79-6401
 Stern, M. P., 79-6571
 Stern, R. S., 79-6071
 Stevens, C., 79-6134
 Stevens, R. H., 79-6231
 Stewart, B. W., 79-6040
 79-6207
 Stich, H. F., 79-6137, 79-6138
 79-6140, 79-6141, 79-6224
 Stillman, D., 79-6038
 Stinson, S. F., 79-6233
 Stone, J. P., 79-6299
 Stoner, G. D., 79-6315
 Stout, R. D., 79-6083
 Strasser, A. L., 79-6115
 Strauss, L. T., 79-6574
 Strnad, B. C., 79-6424
 Strober, S., 79-6469, 79-6471
 79-6472
 Studd, J. W., 79-6348
 Sturdee, D. W., 79-6348
 Subramoniam, S., 79-6582
 Sugano, H., 79-6347, 79-6349
 Sugden, B., 79-6430
 Sugii, S., 79-6490
 Sugimura, T., 79-6146
 Sukumar, S., 79-6236
 Summers, J. E., 79-6345
 Sunderman, F. W., 79-6499
 Sundler, F., 79-6539
 Suzangar, M., 79-6280
 Svoboda, D. J., 79-6153
 Sweatman, T. W., 79-6253
 Swerczek, T. W., 79-6258
 Swern, D., 79-6245
 Syrjanen, K. J., 79-6549
 Szymczyk, T., 79-6199
 Takahashi, M., 79-6208
 Takahashi, T., 79-6483
 Takamizawa, H., 79-6028
 Takaoka, T., 79-6195
 Takatani, O., 79-6347, 79-6349
 Takayama, S., 79-6328
 Takebe, H., 79-6355
 Takeichi, N., 79-6509
 Takeishi, K., 79-6166
 Takeo, K., 79-6490
 Taketomi, M., 79-6180
 Takeyama, H., 79-6479
 Takiuchi, Y., 79-6481
 Tamasi, P., 79-6354
 Tamura, K., 79-6221, 79-6222
 Tancer, M. L., 79-6552
 Tanimura, A., 79-6180
 Tarone, G., 79-6388
 Tashiro, F., 79-6257
 Tate, M. E., 79-6230
 Tatsumi, E., 79-6481
 Taupp, W., 79-6340
 Taylor, A. M., 79-6355
 Taylor, J. M., 79-6061
 Tennant, R. W., 79-6460
 Teplitz, R. L., 79-6358
 Territo, M., 79-6474
 Terzaghi, M., 79-6276
 Terzian, J., 79-6482
 Tesoro-Tess, J. D., 79-6562
 Tevethia, M. J., 79-6076
 Tevethia, S. S., 79-6076
 Thakker, D. R., 79-6017
 79-6308, 79-6334
 Thenot, J. P., 79-6254
 Theodoropoulos, G., 79-6543
 Thibodeau, L. A., 79-6071
 Thilly, W. G., 79-6326
 Thissen, M. R., 79-6173
 Thom, M. H., 79-6348
 Thomas, P. E., 79-6304
 Thompson, H. J., 79-6200
 Thompson, J. L., 79-6428
 Thorbecke, G. J., 79-6363
 Thorgeirsson, S. S., 79-6167
 Thorgiersson, S. S., 79-6314
 Thust, R., 79-6256
 Tierney, B., 79-6293, 79-6309
 79-6312
 Tines, S., 79-6196
 Tjälve, H., 79-6142, 79-6183
 Todaro, G. J., 79-6267, 79-6400
 Todd, R. B., 79-6351
 Toga, M., 79-6320
 Tokuno, S., 79-6356
 Tom, B. H., 79-6087
 Toole, B. P., 79-6389
 Torhorst, J., 79-6123, 79-6125
 Torres, J. E., 79-6426
 Toyama, Y., 79-6271
 Traub, N. R., 79-6173
 Traut, H., 79-6365
 Trentin, J. J., 79-6079
 Tripiet, M. F., 79-6320
 79-6321
 Trouet, A., 79-6229
 Troxler, D. H., 79-6407
 Truhaut, R., 79-6106, 79-6343
 79-6344
 Trump, B. F., 79-6315
 Tsubura, A., 79-6302
 Tsuchida, N., 79-6406
 Tsukada, H., 79-6171
 Tudek, B., 79-6199
 Tuffrey, M., 79-6366, 79-6404
 Tuyns, A. J., 79-6565
 Tyihak, E., 79-6059
 Tyler, C. W., 79-6574
 Uchino, H., 79-6481
 Udupa, R. S., 79-6063
 Ueno, Y., 79-6257
 Umans, R. S., 79-6282
 Underwood, P. B., 79-6577
 Upcroft, P., 79-6442
 Vaage, J., 79-6515
 Vachalkova, A., 79-6330
 Vacquier, J. P., 79-6397
 Vagnozzi, R., 79-6529
 Vahakangas, K., 79-6322
 Vainio, H., 79-6248
 Vaishnav, Y., 79-6007
 Van Duuren, B. L., 79-6150
 van Gemert, P. J., 79-6323
 Van Ryzin, J., 79-6033
 Van Tassel, R. L., 79-6575
 Varela-Duran, J., 79-6535
 Varela-Nunez, R., 79-6535
 Varga, L., 79-6354
 Varmus, H. E., 79-6380
 Varricchio, F., 79-6508
 Vaught, J. B., 79-6296
 Vedrenne, C., 79-6321
 Venter, P. F., 79-6055
 Verma, I. M., 79-6415
 Vesco, C., 79-6600
 Veselovskaia, T. V., 79-6402
 Vesselinovitch, S. D., 79-6581
 Vidali, G., 79-6177, 79-6600
 Vilholm, H. E., 79-6524
 Vita, R., 79-6182
 Vitetta, E. S., 79-6472
 Vogel, E., 79-6158, 79-6205
 79-6209
 Vogt, P. K., 79-6384
 Vohra, S. K., 79-6245
 Volfson, N. I., 79-6251
 Volterrani, F., 79-6562
 Vomvovanni, V. E., 79-6159
 von Bahr, C., 79-6167
 von Borstel, R. C., 79-6163
 Vose, C. W., 79-6303
 Vostrova, N. G., 79-6227
 Vutuc, C., 79-6584
 Wade-Evans, T., 79-6348
 Waggenspack, C., 79-6570
 Waksal, S. D., 79-6083
 Walker, A. R., 79-6575
 Wallcave, L., 79-6196
 Walsh, C., 79-6333
 Walsh, P. J., 79-6371
 Wang, M., 79-6197
 Wang, Y., 79-6197
 Ward, J. M., 79-6541
 Warnke, R. A., 79-6469
 Warnock, M. L., 79-6569
 Warren, S., 79-6351
 Wassermann, D., 79-6112
 Wassermann, M., 79-6112
 Watanabe, K., 79-6204
 Watanabe, T., 79-6135
 Weber, J., 79-6455, 79-6457
 Weeks, M. O., 79-6411
 Wehle, H. E., 79-6120
 Wei, L., 79-6141
 Weichselbaum, R. R., 79-6377
 Weigert, J., 79-6279
 Weill, H., 79-6570
 Weimar, V. M., 79-6473
 Weinhouse, S., 79-6149
 Weinstein, I. B., 79-6268
 79-6272, 79-6277, 79-6278
 79-6335
 Weisburger, E. K., 79-6262
 Weisburger, J. H., 79-6204
 Weiss, D. W., 79-6476
 Weissman, I. L., 79-6469
 Wells, B. C., 79-6174
 Wells, S. A., 79-6547
 Welsch, C. W., 79-6027
 Werczberger, R., 79-6261
 Werko, L., 79-6060
 West, C. M., 79-6271
 White, P. J., 79-6348
 White, W. E., 79-6139
 Whiting, R. F., 79-6137
 79-6138, 79-6141
 Wiencke, J. K., 79-6143
 Wiessler, M., 79-6148
 Wilhelm, R., 79-6186
 Wilkins, T. D., 79-6575
 Will, L. A., 79-6231
 Williams, D. C., 79-6339
 Williams, D. R., 79-6559
 Williams, G. M., 79-6034
 Williams, K. A., 79-6585
 Williams, R. M., 79-6348
 Williamson, R. C., 79-6378
 Winawer, S. J., 79-6550
 Wise, A., 79-6280
 Witte, O. N., 79-6403
 Wittliff, J. L., 79-6346
 Wittner, D., 79-6466
 Wivel, N. A., 79-6394
 Wold, W. S., 79-6451, 79-6454
 Wolf, M. H., 79-6182
 Wolff, B., 79-6580
 Wolff, D. J., 79-6164
 Wood, A. W., 79-6015, 79-6017
 79-6304, 79-6308, 79-6334
 Wood, J. L., 79-6290
 Wood, W. C., 79-6513
 Woodward, J. G., 79-6494
 Worden, A. N., 79-6104
 Yagi, H., 79-6015, 79-6017
 79-6304
 Yamada, K., 79-6479
 Yamada, M., 79-6328
 Yamada, T., 79-6180
 Yamagiwa, J., 79-6367
 Yamamoto, K., 79-6226
 Yamamoto, M., 79-6180
 Yamamoto, N., 79-6431
 Yamamoto, T., 79-6414
 Yamamura, Y., 79-6470
 Yamasaki, H., 79-6278
 Yang, S. S., 79-6394
 Yaniv, A., 79-6461
 Yanovich, S., 79-6480
 Yeung, K. Y., 79-6133
 Yih-van de Hurk, E. W., 79-6323
 Yogeewaran, G., 79-6538
 Yoshida, T. O., 79-6498
 Young, J. K., 79-6409
 Young, H., 79-6412
 Young, H. A., 79-6411
 Young, L. J., 79-6396
 Young, R. J., 79-6097
 Yu, H., 79-6548
 Yuasa, Y., 79-6414
 Yutani, C., 79-6459
 Zachary, R. B., 79-6555
 Zachau, H. G., 79-6491
 Zarudin, V. V., 79-6485
 Zasukhina, G. D., 79-6227
 Zaviacic, M., 79-6218
 Zdzienicka, M., 79-6199
 Zech, L., 79-6145
 Zedeck, M. S., 79-6148
 Zeiger, E., 79-6243
 Zelle, B., 79-6355
 Zeller, W. J., 79-6211
 Zembrzycka, H., 79-6121
 Zern, R. T., 79-6547
 Zielenska, M., 79-6199
 Ziemei, F., 79-6442
 Zimmer, A., 79-6461
 zur Hausen, H., 79-6420

LIBRARY U. OF I. URBANA - CHAMPAIGN

Subject Index

Abdominal Neoplasms
 Burkitt's Lymphoma
 Nonendemic Disease, 79-6524
 Lymphangioma
 Radiation, Ionizing, 79-6370
 Lymphangiosarcoma
 Neoplasm Recurrence, Local, 79-6370

Abnormalities
 Nephroblastoma
 Neoplasms, Multiple Primary, 79-6546
 Sex Hormones
 Epidemiology, Review, 79-6116
 Teratogenic Effect, Review, 79-6116
 4,4'-Stilbenediol, α,α' -Diethyl-
 Epidemiology, Review, 79-6025

Acetamide, N-Fluoren-2-yl-
 Ames Test
 Mutagenic Activity, 79-6169
 Mutagenic Metabolite, 79-6167
 S9 Fraction, Guinea Pig, 79-6166
 7,8-Benzoflavone
 Ames Test, 79-6166
 Cytochrome P-450
 Ames Test, 79-6166
 Dimethylamine, N-Nitroso-
 DNA Repair, 79-6170
 Guanine, 7-Methyl-
 DNA Repair, 79-6170
 Hepatoma
 Alpha Fetoproteins, 79-6172
 Neoplasm Transplantation, 79-6172
 Microsomes, Liver
 Mutagenic Metabolite, 79-6167
 Peptides, 79-6167
 NADPH Cytochrome C Reductase
 Ames Test, 79-6166
 Photosensitive Analogs
 Carcinogenic Potential, 79-6139
 Purine, 2-Amino-6-methoxy-
 DNA Repair, 79-6170
 Liver, Rat, 79-6170

Acetamide, N,N'-Fluorene-2,7-diylbis-
 Liver Neoplasms
 Histochemical Study, Peroxisomes
 79-6171
 Precancerous Conditions, 79-6171

Acetamide, N-(7-Hydroxyfluoren-2-yl)-
 Aryl Hydrocarbon Hydroxylases
 Microsomes, Liver, 79-6167

Acetanilide, 4'-Hydroxy-
 Cysteine
 Hepatotoxic Metabolite, Review
 79-6007
 Glutathione
 Hepatotoxic Metabolite, Review
 79-6007

**Acetic Acid, (Ethylenebis(oxyethylenetri-
 lilo))tetra-**
 Glioma
 Calcium, 79-6164

**Acetic Acid, Methylnitrosaminomethyl Es-
 ter**
 Mutagenic Metabolite
 Tissue Specificity, 79-6165
 Pyrazole
 Toxicity, Rat, 79-6148

Acetohydroxamic Acid, N-4-Biphenyl-
 Acyltransferases
 Mammæ, Rat, 79-6173

Acetohydroxamic Acid, N-Fluoren-2-yl-
 Acyltransferases
 Mammæ, Rat, 79-6173
 RNA, Ribosomal, Binding, 79-6173
 Aryl Hydrocarbon Hydroxylases
 Microsomes, Liver, 79-6167
 Chromatin

Acetohydroxamic Acid, N-Fluoren-2-yl-
 (cont'd)
 Binding Sites, Liver, 79-6168
 DNA Adduct, 79-6168
 Metabolism
 Pharmacokinetics, Review, 79-6008

Acetonitrile, 2,2'-Iminobis-
 Ascorbic Acid
 Nitrosation, 79-6245

p-Acetophenetidine
 Glutathione
 Hepatotoxic Metabolite, Review
 79-6007
 Metabolism
 Pharmacokinetics, Review, 79-6008

Acetyl Chloride, Dichloro-
 Ethylene, Trichloro-
 Epoxide Metabolites, 79-6151

Achlorhydria
 Stomach Neoplasms
 Epidemiology, 79-6561

Acid Phosphatase
 Glioma
 Enzymatic Activity, 79-6201
 Leukemia, Hairy Cell
 Diagnosis, 79-6482
 Phagocytosis, 79-6525

Acridine
 DNA Repair
 Carcinogenic Potential, Review
 79-6013
 Mutation
 Genetic Effects, Review, 79-6013

Acridine, 9-Amino-
 Poly U
 DNA, Binding, 79-6265

Acridine, 3,6-Bis(dimethylamino)-
 Poly U
 DNA, Binding, 79-6265

Acridine, 3,6-Diamino-
 Carcinosarcoma
 Light, 79-6287
 Lymphoma
 Light, 79-6287
 Mammary Neoplasms, Experimental
 Light, 79-6287
 Poly U
 DNA, Binding, 79-6265
 Skin Neoplasms
 Light, 79-6287

Acridino(2,1,9-mna)acridine
 Carcinogenic Activity
 Polarographic Behavior, 79-6330

Acrolein, 2-Chloro-
 Carbamic Acid, Diisopropylthio-, S-(2,3-
 Dichloroallyl) Ester
 Mutagenic Metabolite, 79-6056

Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 Ames Test
 Mutagenic Activity, Review, 79-6046

Acrylonitrile
 Brain Neoplasms
 Carcinogenic Activity, Rat, 79-6181
 Occupational Hazard
 Risk Factors, 79-6181

Actinomycin D
 Amino Acids
 Liver, Rat, 79-6598

Acyltransferases
 Acetohydroxamic Acid, N-4-Biphenyl-
 Mammæ, Rat, 79-6173
 Acetohydroxamic Acid, N-Fluoren-2-yl-

Acyltransferases (cont'd)
 Mammæ, Rat, 79-6173
 RNA, Ribosomal, Binding, 79-6173

Adenine Nucleotides
Agrobacterium tumefaciens
 Bacteriocins, 79-6230

Adenocarcinoma
 Colonic Neoplasms
 Hydrazine, 1,2-Dimethyl-, 79-6177
 Immunity, Cellular, Review, 79-6087
 Immunotherapy, Review, 79-6087
 Urea, Methyl Nitroso-, 79-6208
 Dipropylamine, 2-Hydroxy-N-nitroso-2'-
 oxo-
 Neoplasm Metastasis, 79-6196
 Ear Neoplasms
 Pectin, 79-6176
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Age Factors, Rat, 79-6223
 Cells, Cultured, 79-6220
 Precancerous Conditions, 79-6221
 Gynecologic Neoplasms
 Hemorrhage, 79-6551
 Hydrazine, 1,2-Dimethyl-
 Nucleoproteins, 79-6177
 Pectin, 79-6176
 Intestinal Neoplasms
 Hydrazine, 1,2-Dimethyl-, 79-6175
 79-6176
 Polyps, 79-6175
 Kidney Neoplasms
 Anthraquinone, 1-Amino-2-methyl-
 79-6262
 T-Lymphocytes
 Antibody Formation, 79-6517
 79-6518
 Hypersensitivity, 79-6517, 79-6518
 Lymphocyte Depletion, 79-6517
 79-6518
 Neoplasm Metastasis, 79-6517
 Mammary Neoplasms, Experimental
 Antibody-Dependent Cell Cytotoxicity
 79-6518
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6299
 Lymphocyte Depletion, 79-6517
 79-6518
 Neoplasm Metastasis, 79-6517
 Radiation, Ionizing, 79-6299, 79-6517
 79-6518
 p-Toluamide, N-Isopropyl- α -(2-
 methylhydrazino)-, 79-6299
 Virus, Murine Mammary Tumor
 79-6396
 Water Pollutants, 79-6343, 79-6344
 Ovarian Neoplasms
 Water Pollutants, 79-6343
 Pancreatic Neoplasms
 Dipropylamine, 2-Hydroxy-N-nitroso-
 2'-oxo-, 79-6196
 Prostatic Neoplasms
 Androst-4-ene-3,17-dione, 79-6351
 Precancerous Conditions, 79-6553
 Testosterone, 79-6351
 Psoralen, 8-Methoxy-
 Ultraviolet Rays, 79-6287
 Radiation, Ionizing
 Hypersensitivity, 79-6518
 Neoplasm Metastasis, 79-6517
 4,4'-Stilbenediol, α,α' -Diethyl-
 Epidemiology, Review, 79-6025
 Stomach Neoplasms
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-6221, 79-6222, 79-6223
 Propionic Acid, 2-(p-Chlorophenoxy)-
 2-methyl-, Ethyl Ester, 79-6153
 Urea, 1-(2-Chloroethyl)-3-(2-
 hydroxyethyl)-1-nitroso-
 Drug Therapy, 79-6211
 Urogenital Neoplasms
 Propionic Acid, 2-(p-Chlorophenoxy)-

Adenocarcinoma (cont'd)
 2-methyl-, Ethyl Ester, 79-6153
Uterine Neoplasms
 Adenosine, Methyl Nitroso-, 79-6232
 Case Report, Ovariectomy, 79-6552
 Contraceptives, Oral, 79-6577
 Estrogens, 79-6567, 79-6577
 Estrone, 79-6028
 FSH, 79-6552
 LH, 79-6552
 Progesterational Hormones, 79-6028
 Receptors, Hormone, Review, 79-6028
Vaginal Neoplasms
 Epidemiology, Review, 79-6125
 4,4'-Stilbenediol, α,α' -Diethyl-, 79-6125
 Virus, Murine Mammary Tumor
 Antigens, Viral, 79-6396

Adenofibroma
 Mammary Neoplasms, Experimental
 Radiation, Ionizing, 79-6299
 Morpholine, *N*-Nitroso-
 Carcinogenic Activity, Rat, 79-6215

Adenolymphoma
 Cell Transformation, Neoplastic
 Case Report, 79-6519

Adenoma
Adrenal Gland Neoplasms
 Strain Difference, Hamster, 79-6544
Colonic Neoplasms
 Urea, Methyl Nitroso-, 79-6208
Gastrointestinal Neoplasms
 Precancerous Conditions, Review
 79-6101
IgG
 Antigen-Antibody Complex, 79-6505
Intestinal Neoplasms
 Hydrazine, 1,2-Dimethyl-, 79-6176
Liver Neoplasms
 Phorbol, 79-6189
 Phorbol, 12-Deoxy-, 79-6189
Lung Neoplasms
 Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-, 79-6017
 Cholanthren-2-ol, 3-Methyl-, 79-6308
 Cholanthren-2-one, 3-Methyl-, 79-6308
 Cholanthrene, 9,10-Dihydro-3-methyl-1,9,10-trihydroxy-, 79-6308
 Mouse, 79-6541
 Phorbol, 79-6266
Pancreatic Neoplasms
 Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
Pituitary Neoplasms
 Imidazole-1-ethanol, 2-Methyl-5-nitro-79-6216
Stomach Neoplasms
 Classification, Review, 79-6094
 Guanidine, 1-Methyl-3-nitro-1-nitroso-79-6222
Thyroid Neoplasms
 Radiation, Ionizing, 79-6113, 79-6368
 Strain Difference, Hamster, 79-6544

Adenomatosis, Familial Endocrine
 Carcinoid Tumor
 Genetics, Review, 79-6093
Gastrointestinal Neoplasms
 Epidemiology, Review, 79-6100
Parathyroid Neoplasms
 Genetics, Review, 79-6093
Thyroid Neoplasms
 Genetics, Review, 79-6093

Adenosine Cyclic 3',5' Monophosphate
 Glioma
 Calcium, 79-6164
 Norepinephrine, 79-6164
Mesothelioma
 Asbestos, 79-6231

Adenosine, Methyl Nitroso-
 Lung Neoplasms
 Carcinogenic Activity, Mouse, 79-6232
 Mammary Neoplasms, Experimental

Adenosine, Methyl Nitroso- (cont'd)
 Carcinoma, 79-6232
Nitrous Acid
 Carcinogenic Activity, Mouse, 79-6232
 Nucleoside Interaction, 79-6232
Uterine Neoplasms
 Adenocarcinoma, 79-6232

Adenosine Triphosphatase
 Virus, SV40
 Antigens, Neoplasm, 79-6441

Adrenal Cortex
 Kepone
 Carcinogenic Potential, Review
 79-6005
 Mirex
 Carcinogenic Potential, Review
 79-6005

Adrenal Gland Neoplasms
 Adenoma
 Strain Difference, Hamster, 79-6544
 Smoke Condensate
 Hyperplasia, 79-6285

Adrenergic Beta Receptor Agonists
 Glioma
 Calcium, 79-6164

Aflatoxin B1
 Cell Division
 Gene Deletion, Review, 79-6019
 Corn Oil
 Enzyme Activation, 79-6279
 Dietary Proteins
 Alkaline Phosphatase, 79-6280
 Aminotransferases, 79-6280
 Lactate Dehydrogenase, 79-6280
DNA, Binding
 Liver, Rat, Review, 79-6021
Food Contamination
 Fruit, 79-6281
Hepatoma
 Corn Oil, 79-6279
 Dietary Fats, 79-6279
 Lactate Dehydrogenase
 Precancerous Conditions, 79-6280
Liver Neoplasms
 Precancerous Conditions, 79-6280
Nucleic Acids
 Mutagenic, Carcinogenic Metabolite, Review, 79-6020
 Retinol
 Metabolism, Review, 79-6019
 Steroids
 Chromosomes, Review, 79-6019

Aflatoxin G1
 Food Contamination
 Fruit, 79-6281

Aflatoxin M1
 Dietary Proteins
 Metabolism, Rat, 79-6280

Aflatoxin P1
 Dietary Proteins
 Metabolism, Rat, 79-6280

Agglutination
 12-*O*-Tetradecanoylphorbol-13-acetate
 Lymphocytes, 79-6269

Aging
 Amyloid
 Liver, Spleen, 79-6492
 Paraproteinemia
 T-Lymphocytes, 79-6467

Agrobacterium tumefaciens
 Adenine Nucleotides
 Bacteriocins, 79-6230
 Amino Acids
 Plasmids, Review, 79-6037
 Bacteriocins
 Structure-Activity Relationship
 79-6230
DNA, Bacterial
 Transformation, Genetic, 79-6037

Agrobacterium tumefaciens (cont'd)
 Plant Tumors
 Bacteriocins, 79-6230
 Plasmids, Review, 79-6037

Air Pollutants
 Thresholds
 Risk Evaluation, Review, 79-6106

Air Pollution
 Beryllium
 Epidemiology, Review, 79-6105
 Carcinogen, Chemical
 Bioassays, 79-6263
 Carcinogen, Environmental
 Epidemiology, Review, 79-6104
 Chromium
 Epidemiology, Review, 79-6105
 Dimethylamine, *N*-Nitroso-
 Occupational Hazard, 79-6182
 Fluorescein, Disodium Salt
 Occupational Hazard, 79-6263
 Lung Neoplasms
 Nickel, 79-6054
 Mesothelioma
 Asbestos, 79-6105
 Morpholine, *N*-Nitroso-
 Occupational Hazard, 79-6182
 Nickel
 Epidemiology, Review, 79-6105
 Nitrosamines
 Carcinogenic Potential, 79-6182
 Plutonium
 Nuclear Reactors, 79-6374

Alanine Aminotransferase
 Carbon Tetrachloride
 Serum Levels, 79-6147
 Isopropyl Alcohol
 Serum Levels, 79-6147
 Methanol
 Serum Levels, 79-6147

Alanine, 3-(*p*-(Bis(2-chloroethyl)amino)phenyl)-
 Leukemia, Myeloblastic
 Drug Therapy, 79-6009

Albumins
 Hepatoma
 Cells, Cultured, 79-6597

Alcoholic Beverages
 Digestive System Neoplasms
 Epidemiology, Australia, 79-6586
 Epidemiology
 Japan, 79-6564
Esophageal Neoplasms
 Carcinoma, 79-6566
 Epidemiology, 79-6564, 79-6565
 Epidemiology, Britain, 79-6560
Neoplasms
 Epidemiology, Review, 79-6022
Prostatic Neoplasms
 Epidemiology, 79-6564
Rectal Neoplasms
 Epidemiology, 79-6564

Aldrin
 Carcinogenic Activity
 Mouse, Rat, Review, 79-6010
 Diet
 Hepatocarcinogenesis, 79-6259

Alkaline Phosphatase
 Aflatoxin B1
 Dietary Proteins, 79-6280
 Bladder Neoplasms
 Cell Division, Review, 79-6095

Alkylating Agents
 DNA Repair
 Mutation, Review, 79-6067
 Kidney Neoplasms
 DNA Repair, Review, 79-6065
 T-Lymphocytes
 Receptors, Fc, 79-6466
 Nervous System Neoplasms
 DNA Repair, Review, 79-6065
 Xeroderma Pigmentosum

Alkylating Agents (cont'd)
DNA Repair, 79-6067

Alpha 1-Antitrypsin

Cholangioma
Immunohistochemical Study, 79-6542

Hepatoma

Alpha Fetoproteins, 79-6542
Immunohistochemical Study, 79-6542

Alpha Fetoproteins

Hepatoma

Acetamide, *N*-Fluoren-2-yl-, 79-6172
Alpha 1-Antitrypsin, 79-6542
Benzenamine, 2-Methyl-4-((2-methylphenyl)azo)-, 79-6234
Cells, Cultured, 79-6597
Chlordane, 79-6172
Precancerous Conditions, 79-6234
Teratoid Tumor
Cell Differentiation, Review, 79-6089

Alpha Particles

Breast Neoplasms

Theoretical Model, Review, 79-6070

Plutonium

Collagen, 79-6372
Lung, Hamster, 79-6372
Radioactive Fallout
Theoretical Model, Review, 79-6070

Americium

Body Burden

Inhalation Study, Dog, 79-6375

Bone and Bones

Half-Life, 79-6375

Ames Test

Acetamide, *N*-Fluoren-2-yl-
7,8-Benzoflavone, 79-6166
Cytochrome P-450, 79-6166
Mutagenic Activity, 79-6169
Mutagenic Metabolite, 79-6167
NADPH Cytochrome C Reductase
79-6166
S9 Fraction, Guinea Pig, 79-6166
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
Mutagenic Activity, Review, 79-6046
1-Anthracenamide
Mutagenic Activity, 79-6169
2-Anthracenamide
Microsomes, Intestinal Mucosa
79-6178
Mutagenic Activity, 79-6169
Benz(a)anthracene
Dihydrodiol Metabolites, 79-6293
Benz(a)anthracene, 7,12-Dimethyl-
Dihydrodiol Metabolites, 79-6293
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-6301
Benz(a)anthracene, 7-Methyl-
Dihydrodiol Metabolites, 79-6293
1,3-Benzenediamine, 4-Methoxy-
Mutagenic Metabolite, 79-6167
S9 Fraction, Liver, Kidney, 79-6235
Benzo(a)pyrene
Dihydrodiol Metabolites, 79-6293
Hepatocytes, 79-6323
Microsomes, Liver, 79-6318
Soot Extract, 79-6326
trans-Stilbene Oxide, 79-6316
Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
7,8,9,10-tetrahydro-
Aroclor 1254, 79-6335
Barbituric Acid, 5-Ethyl-5-phenyl-
79-6335
Cholanthrene, 3-Methyl-, 79-6335
DNA Adducts, 79-6335
Benzo(a)pyrene 4,5-Oxide
Enantiomers, 79-6334
2,3-Butanedione
Mutagenic Activity, 79-6160
Carcinogen, Chemical
Bioassays, Review, 79-6048
Chlorophyll, 79-6131
Microsomes, Liver, 79-6242
Carcinogen, Environmental

Ames Test (cont'd)

Mutagenic Activity, Review, 79-6016
Cholanthrene, 3-Methyl-
Dihydrodiol Metabolites, 79-6293
Cholesterol
Autooxidation Products, 79-6337
Mutagenic Activity, 79-6337
Chrysene, 1,2-Dihydroxy-3,4-oxy-1,2,3,4-tetrahydro-
Mutagenic Activity, 79-6304
Chrysene, 3-Fluoro-5-methyl-
Mutagenic Activity, 79-6305
Chrysene, 7-Fluoro-5-methyl-
Mutagenic Activity, 79-6305
Cycasin
Beta-Glucosidases, 79-6146
Enzyme Activation, 79-6146
1,2-Cyclohexanedione
Mutagenic Activity, 79-6160
Cyclopenta(cd)pyrene
Soot Extract, 79-6326
Dibenzo(a,i)pyrene
Mutagenic Activity, 79-6169
Disulfide, Bis(dimethylthiocarbamoyl)-
Mutagenic Activity, 79-6199
S9 Fraction, 79-6199
Ethane, 1,2-Dibromo-
Mutagenic Activity, Review, 79-6046
Ethane, 1,2-Dichloro-
Mutagenic Activity, Review, 79-6046
Ethylene, Chloro-
Microsomes, Liver, 79-6151
Mutagenic Metabolite, 79-6165
Ethylene, 1,1-Dichloro-
Microsomes, Liver, 79-6151
Ethylene, 1,2-Dichloro-
Microsomes, Liver, 79-6151
Ethylene, Tetrachloro-
Microsomes, Liver, 79-6151
Fluoranthene
Soot Extract, 79-6326
Fluoren-2-amine
Microsomes, Intestinal Mucosa
79-6178
Mutagenic Activity, 79-6169
Mutagenic Metabolite, 79-6167
S9 Fraction, Liver, Kidney, 79-6235
Fluorescent Dyes
Mutagenic Activity, Review, 79-6018
Glyoxal
Mutagenic Activity, 79-6160
Hair Dyes
Mutagenic Activity, Review, 79-6046
Mefloquine Hydrochloride
Mutagenic Activity, 79-6228
Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
Beta-Glucosidases, 79-6146
Methanol, (Methyl-*ONN*-azoxy)-
Beta-Glucosidases, 79-6146
Morpholine, *N*-Nitroso-
Mutagenic Metabolite, 79-6165
Mutagens
Bioassays, Review, 79-6048
Feces, 79-6575
S9 Fraction, 79-6157
1,4-Naphthalenedione, 2-Hydroxy-
Mutagenic Activity, 79-6261
Pararosaniline
Microsomes, Liver, 79-6242
Perylene
Soot Extract, 79-6326
Petroleum
Shale Oil Products, 79-6130
Phenanthrene, 1,2-Dihydroxy-3,4-epoxy-
1,2,3,4-tetrahydro-
Mutagenic Activity, 79-6304
Phthalazine, 1-Hydrazino-
Acetone Condensation Product
79-6254
Mutagenic Activity, 79-6254
Piperazine, 1-Methyl-4-nitroso-
Mutagenic Metabolite, 79-6165
1-Propanol, 2,3-Dibromo-, Phosphate
Mutagenic Activity, Review, 79-6046
4*H*-Pyran-4-one, 5-Hydroxy-
2-(hydroxymethyl)-

Ames Test (cont'd)

Mutagenic Activity, 79-6160
4*H*-Pyran-4-one, 3-Hydroxy-2-methyl-,
2-Ethyl Ester
Mutagenic Activity, 79-6160
4*H*-Pyran-4-one, 3-Hydroxy-2-methyl-
Mutagenic Activity, 79-6160
Quinoline, 7-Chloro-4-(((4-diethylamino)-
1-methylbutyl)amino)-
Mutagenic Activity, 79-6228
Rhodamine B
Mutagenic Activity, 79-6264
Rhodamine 6G
Mutagenic Activity, 79-6264
Sodium Azide
Mutagenic Metabolite, 79-6144
4,4'-Stilbenediol, α,α' -Diethyl-
Carcinogenic Metabolite, 79-6341
p-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-
Mutagenic Activity, 79-6243
m-Toluidine, *N,N*-Dimethyl-
4-(phenylazo)-
Microsomes, Liver, 79-6242
Toxaphene
Mutagenic Activity, Review, 79-6002
s-Triazolo(3,4-*a*)phthalazine-3-methanol
Mutagenic Activity, 79-6254
Urea, (4-Nitrophenyl)-
Nitrosamides, 79-6202

Amino Acids

Actinomycin D
Liver, Rat, 79-6598
Agrobacterium tumefaciens
Plasmids, Review, 79-6037
Cycloheximide
Liver, Rat, 79-6598
Glioma
Nucleic Acids, 79-6201
Hepatoma
Biological Transport, 79-6598
Isobutyric Acid, α -Amino-, 79-6598
Sodium, 79-6598
Isobutyric Acid, α -Amino-
Liver, Rat, 79-6598
Mammary Neoplasms, Experimental
Diet, Review, 79-6041
Neoplasm Metastasis
Diet, Review, 79-6041
Virus Adeno 2
Peptides, 79-6454

Aminotransferases

Aflatoxin B1
Dietary Proteins, 79-6280

Ammonium, (5-Amino-5-carboxypentyl)trimethyl-

Neoplasms, Experimental
Growth, Review, 79-6059

Amyloid

Aging
Liver, Spleen, 79-6492
Casein
Isolation and Characterization, Mouse
79-6492
Endotoxins
Isolation and Characterization, Mouse
79-6492
Plasmacytoma
IgG, 79-6492

Androgens

Breast Neoplasms
Receptors, Hormone, 79-6349
Prostatic Neoplasms
Parabiosis, 79-6351

Androst-4-ene-3,17-dione

Prostatic Neoplasms
Adenocarcinoma, 79-6351

Anemia, Aplastic

Ataxia Telangiectasia
DNA Repair, Review, 79-6067
DNA Repair
Chromosome Aberrations, Review

Anemia, Aplastic (cont'd)
Chromosome Aberrations, Review
79-6092

Angiosarcoma
Anthraquinone, 2-Amino-
Carcinogenic Activity, Mouse, 79-6262

**Aniline, *N,N*-Dimethyl-
Smoke Condensate**
Aromatic Amines, 79-6241

**Aniline, *N,N*-Dimethyl-*p*-phenylazo-
Blood Proteins**
Binding, 79-6247
Hepatoma
Antigens, Neoplasm, 79-6310
Immune Serums, 79-6507
Lipoproteins
Binding, 79-6247
Porphyria
Hepatocarcinogenesis, Review
79-6005

**Aniline, *N*-Ethyl-
Smoke Condensate**
Aromatic Amines, 79-6241

**Aniline, *N*-Ethyl-*p*-(phenylazo)-
Liver Neoplasms**
Hydroxy Derivative, 79-6246

**Aniline, *N*-Methyl-
Ascorbic Acid**
Nitrosation, 79-6245

**Aniline, *N*-Methyl-*p*-(phenylazo)-
Hepatoma**
Barbituric Acid, 5-Ethyl-5-phenyl-
79-6246
Liver
Binding, 79-6237

**Aniline, *p*-(Phenylazo)-
Cell Transformation, Neoplastic**
Carcinogenic Metabolite, 79-6288
Liver
Binding, 79-6237
Liver Neoplasms
Hydroxy Derivative, 79-6246

1-Anthracenamide
Ames Test
Mutagenic Activity, 79-6169

2-Anthracenamide
Ames Test
Microsomes, Intestinal Mucosa
79-6178
Mutagenic Activity, 79-6169
Bacteroides fragilis
Mutagenic Metabolite, 79-6178

**Anthranilic Acid, *N*-(α,α,α -Trifluoro-*m*-
tolyl)-
12-*O*-Tetradecanoylphorbol-13-acetate
Prostaglandins E, 79-6274**

**Anthraquinone, 2-Amino-
Angiosarcoma**
Carcinogenic Activity, Mouse, 79-6262
Hepatoma
Carcinogenic Activity, Mouse, 79-6262
Diet, 79-6262

**Anthraquinone, 1-Amino-2-methyl-
Hepatoma**
Carcinogenic Activity, Rat, 79-6262
Kidney Neoplasms
Adenocarcinoma, 79-6262
Nephritis, Interstitial
Diet, 79-6262

**Anthraquinone, 2-Methyl-1-nitro-
Hepatoma**
Carcinogenic Activity, Mouse, 79-6262
Soft Tissue Neoplasms
Fibroma, 79-6262

Anti-Antibodies
Plasmacytoma
IgA, 79-6489

Anti-Antibodies (cont'd)
Virus, AKR Murine Leukemia
Genetics, 79-6404

Antibodies, Viral
Burkitt's Lymphoma
Virus, Epstein-Barr, 79-6524

Antibody Specificity
Benzenamine, *N,N*-Dimethyl-4-((3-
methylphenyl)azo)-
Carcinogenic Metabolite, 79-6237
Intestinal Neoplasms
Isoantigens, 79-6513
Leukemia
Histocompatibility Antigens, 79-6477
Leukemia, Hairy Cell
B-Lymphocytes, 79-6480
Monocytes, 79-6480
Multiple Myeloma
Antigens, 79-6504
Virus, Bovine Papilloma
Viral Proteins, 79-6420
Virus, Rous Sarcoma
Antigens, 79-6388

Antigen-Antibody Complex
Adenoma
IgG, 79-6505
Chordoma
IgG, 79-6505
Melanoma
IgG, 79-6505
Virus, Avian Sarcoma
Phosphotransferases, ATP, 79-6383
Virus, Murine Sarcoma
Protein Kinase, 79-6400

Antigen-Antibody Reactions
Antigens, Neoplasm
Immunization, Review, 79-6086
Fibrosarcoma
Histocompatibility Antigens, 79-6494
Leukemia, Radiation-Induced
T-Lymphocytes, 79-6483
T-Lymphocytes
Isoantigens, 79-6470
Myeloma Proteins
Dextrans, 79-6490
Virus, Abelson Murine Leukemia
Immune Serums, 79-6403
Virus, Feline Leukemia
Immune Response, 79-6419
Virus, SV40
Antigenic Determinants, 79-6445

Antigenic Determinants
Thymoma
Virus, Murine Leukemia, 79-6083
Virus, Abelson Murine Leukemia
Virus, Moloney Murine Leukemia
79-6403
Virus, Avian Leukosis-Sarcoma
Genes, Viral, Review, 79-6074
Virus, C-Type RNA Tumor
Viral Proteins, 79-6460
Virus, Feline Leukemia
Precancerous Conditions, 79-6419
Virus, Friend Spleen Focus-Forming
Virus, Mink Cell Focus-Inducing
79-6407
Virus, Herpes Gorilla
Virus, Epstein-Barr, 79-6424
Virus, Kirsten Murine Sarcoma
Virus, Harvey Murine Sarcoma
79-6411
Virus, Rous-Associated
Virus, Recombinant, Review, 79-6074
Virus, Rous Sarcoma
Virus, Recombinant, Review, 79-6074
Virus, SV40
Antigen-Antibody Reactions, 79-6445
Virus, Woolly Monkey Sarcoma
Virus, Gibbon Ape Lymphoma
79-6423

Antigens
Multiple Myeloma
Antibody Specificity, 79-6504

Antigens (cont'd)
Isolation and Characterization
79-6504
Neoplasm Metastasis
Tumor Dormancy, Review, 79-6088
Virus, Friend Spleen Focus-Forming
Cell Membrane, 79-6407
Immunity, Cellular, 79-6407
Virus, Recombinant, 79-6407
Virus, Moloney Murine Leukemia
Cell Membrane, Review, 79-6077
Isolation and Characterization
79-6077
Virus, Rous Sarcoma
Antibody Specificity, 79-6388
Cell Membrane, 79-6388
Cell Transformation, Neoplastic
79-6388

Antigens, Neoplasm
Antigen-Antibody Reactions
Immunization, Review, 79-6086
Colonic Neoplasms
Antigen-Antibody Reactions, Review
79-6087

Hepatoma
Aniline, *N,N*-Dimethyl-*p*-phenylazo-
79-6310
Isolation and Characterization
79-6310

Sarcoma
Cholanthrene, 3-Methyl-, 79-6310
Immune Response, 79-6310
Isolation and Characterization
79-6310

Teratoid Tumor
Virus, SV40, 79-6450
Virus, Polyoma
DNA Restriction Enzyme, 79-6439
Virus, SV40

Adenosine Triphosphatase, 79-6441
Antigenic Determinants, Review
79-6076
Deletion Mutants, 79-6447
DNA Replication, 79-6443
Histocompatibility Antigens, 79-6076
Immunoprecipitation, 79-6445
Phenylalanine, 4-Fluoro-, 79-6446
Poly T, 79-6441

Antigens, Viral
Adenocarcinoma
Virus, Murine Mammary Tumor
79-6396
Virus, Epstein-Barr
12-*O*-Tetradecanoylphorbol-13-acetate
79-6431
Virus, Herpes Simplex 1
Lymphocyte Transformation, 79-6426
Virus, Herpes Simplex 2
Lymphocyte Transformation, 79-6426
Virus, Murine Mammary Tumor
Lactation, 79-6396
Precancerous Conditions, 79-6396
Virus, Rous Sarcoma
Cell Transformation, Neoplastic
79-6386

Antilymphocyte Serum
Sarcoma, Reticulum Cell
Immunosuppression, 79-6009

Antipain
Radiation, Ionizing
Cell Transformation, Neoplastic
79-6361

Areca
Mouth Neoplasms
Epidemiology, Review, 79-6099

Arginase
Benzenamine, *N,N*-Dimethyl-4-((3-
methylphenyl)azo)-
Liver, Rat, 79-6236

Arginine
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Chromosome Aberrations, 79-6224

Arginine (cont'd)

- Leukemia, Myelocytic
- Blastic Crises, 79-6592
- Metabolism, 79-6592
- Mitomycin C
- Chromosome Aberrations, 79-6224
- Quinoline, 4-Nitro-, 1-Oxide
- Chromosome Aberrations, 79-6224
- Ultraviolet Rays
- Chromosome Aberrations, 79-6224
- Virus, Adeno 2
- Peptide Hydrolases, 79-6457
- Viral Proteins, 79-6457

Aroclor 1254

- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
- Ames Test, 79-6335
- Chrysene, 1,2-Dihydroxy-3,4-oxy-1,2,3,4-tetrachloro-
- Carcinogenic Metabolite, 79-6305
- Mutagens
- Soot Extract, 79-6326

Arsenic

- Lung Neoplasms
- Occupational Hazard, 79-6115
- Smoking
- Co-carcinogenic Effect, Review 79-6053

Arsenious Acid, Potassium Salt

- Carcinoma, Epidermoid
- Case Report, 79-6132
- Hypercalcemia, 79-6132

Aryl Hydrocarbon Hydroxylases

- Acetamide, *N*-(7-Hydroxyfluoren-2-yl)-
- Microsomes, Liver, 79-6167
- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
- Microsomes, Liver, 79-6167
- Benz(a)anthracene
- Hepatocytes, Hamster, 79-6288
- B-Lymphocytes, 79-6296, 79-6313
- Benz(a)anthracene, 7,12-Dimethyl-
- Enzyme Inhibition, 79-6313
- 1,3-Benzenediamine, 4-Methoxy-
- Cholanthrene, 3-Methyl-, 79-6235
- Benzo(a)pyrene
- Cells, Cultured, 79-6328
- Cytochrome P-450, 79-6318
- DNA, Binding, 79-6318
- B-Lymphocytes, 79-6313
- Cholanthrene, 3-Methyl-
- Hepatocytes, Hamster, 79-6288
- B-Lymphocytes, 79-6313
- Ovary, Mouse, 79-6314
- Chrysene
- Enzyme Inhibition, 79-6313
- Concanavalin A
- B-Lymphocytes, 79-6296
- Dibenz(a,h)anthracene
- 5,6-Benzoflavone, 79-6313
- 7,8-Benzoflavone, 79-6313
- B-Lymphocytes, 79-6296, 79-6313
- Plant Agglutinins, 79-6296
- 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate, 79-6313
- Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester, 79-6313
- Dibenzo-*p*-dioxin
- Chlorinated Analogs, 79-6249
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
- Cells, Cultured, 79-6249
- B-Lymphocytes, 79-6313
- Dibenzofuran
- Chlorinated Analogs, 79-6249
- Ethylene, Chloro-
- Metabolism, Liver, 79-6165
- Fluoren-2-amine
- Cholanthrene, 3-Methyl-, 79-6235
- Lipopolysaccharides
- B-Lymphocytes, 79-6296
- Morpholine, *N*-Nitroso-
- Metabolism, Liver, 79-6165
- Piperazine, 1-Methyl-4-nitroso-
- Metabolism, Liver, 79-6165
- Plant Agglutinins

Aryl Hydrocarbon Hydroxylases (cont'd)

- B-Lymphocytes, 79-6296
- Polychlorobiphenyl Compounds
- Cells, Cultured, 79-6249
- Radiation, Ionizing
- Hepatocytes, Hamster, 79-6288
- Asbestos
- Air Pollution
- Epidemiology, Review, 79-6054
- Gastrointestinal Neoplasms
- Environmental Hazard, 79-6569
- Epidemiology, Review, 79-6052
- Kidney Neoplasms
- Epidemiology, Review, 79-6052
- Lung Neoplasms
- Environmental Hazard, 79-6569
- Occupational Hazard, 79-6115
- Macrophages
- Enzymes, Review, 79-6102
- Mesothelioma
- Adenosine Cyclic 3',5' Monophosphate, 79-6231
- Air Pollution, 79-6105
- Epidemiology, Review, 79-6104
- Guanosine Cyclic 3',5' Monophosphate, 79-6231
- Multiple Myeloma, 79-6133
- IgA, 79-6133
- IgG, 79-6133
- Ovarian Neoplasms
- Occupational Hazard, Review, 79-6123
- Peritoneal Neoplasms
- Mesothelioma, 79-6231
- Respiratory Tract Neoplasms
- Epidemiology, 79-6570
- Epidemiology, Review, 79-6052
- Occupational Hazard, 79-6570
- Smoking
- Co-carcinogenic Effect, Review 79-6052, 79-6053, 79-6054
- Vaginal Preparations
- Carcinogenic Potential, Review 79-6055

Asbestosis

- Leukemia, Lymphocytic
- Case Report, 79-6133
- Multiple Myeloma
- Case Report, 79-6133

Ascorbic Acid

- Acetonitrile, 2,2'-Iminobis-
- Nitrosation, 79-6245
- Aniline, *N*-Methyl-
- Nitrosation, 79-6245
- Benz(a)anthracene-7-methanol, 12-Methyl-
- Oxidation Products, 79-6289
- Benzo(a)pyrene
- Dihydrodiol Metabolites, 79-6333
- Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-
- Dihydrodiol Metabolites, 79-6333
- Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
- Dihydrodiol Metabolites, 79-6333
- Benzo(a)pyrene, 9,10-Dihydro-9,10-dihydroxy-
- Dihydrodiol Metabolites, 79-6333
- Benzo(a)pyrene, 11,12-Dihydro-11,12-dihydroxy-
- Dihydrodiol Metabolites, 79-6333
- Diphenylamine
- Nitrosation, 79-6245
- Nitrosamines
- Nitrous Acid, 79-6245

Asthma

- Occupational Hazard
- Epidemiology, Review, 79-6115

Astrocytoma

- Cerebellar Neoplasms
- Radiation, Ionizing, 79-6376
- Ear Neoplasms
- Radiotherapy, 79-6376

Astrocytoma (cont'd)

- Neoplasms, Multiple Primary
- Carotid Body Tumor, 79-6376
- Spinal Cord Neoplasms
- Urea, Ethyl Nitroso-, 79-6210

Ataxia Telangiectasia

- Anemia, Aplastic
- DNA Repair, Review, 79-6067
- DNA Repair
- Chromosome Aberrations, Review 79-6092
- Leukemia
- DNA Repair, Review, 79-6067

Australia Antigen

- Hepatoma
- Immunologic Technics, 79-6543
- Isolation and Characterization 79-6462
- Peptides, 79-6462
- Virus, Hepatitis, 79-6506
- Liver Cirrhosis
- Immunologic Technics, 79-6543
- Virus, Hepatitis
- Epidemiology, Review, 79-6080

Autoimmune Diseases

- Histocompatibility Antigens
- Antigenic Determinants, Review 79-6084

Autosome Abnormalities

- Neoplasms, Multiple Primary
- Case Report, 79-6540

Azathioprine

- Leukemia
- Case Report, 79-6255
- Hepatitis, 79-6255
- Sarcoma, Reticulum Cell
- Immunosuppression, 79-6009

Bacillus subtilis

- Hydrazine, 1,2-Dimethyl-
- Mutagenic Activity, 79-6174

Bacteria

- 5 β -Cholan-24-oic Acid, 3 α -Hydroxy-, 3 α -Sulfate
- Metabolism, 79-6162
- Oncogenic Viruses
- Virus Activation, 79-6463

Bacteriocins

- Agrobacterium tumefaciens*
- Adenine Nucleotides, 79-6230
- Structure-Activity Relationship 79-6230
- Plant Tumors
- Agrobacterium tumefaciens*, 79-6230

Bacteriophages

- Virus, Harvey Murine Sarcoma
- DNA-DNA Hybridization, 79-6410
- Nucleic Acid Heteroduplexes, 79-6410

Bacteroides fragilis

- 2-Anthracenamide
- Mutagenic Metabolite, 79-6178
- Fluoren-2-amine
- Mutagenic Metabolite, 79-6178

Barbituric Acid, 5-Ethyl-5-phenyl-

- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
- Ames Test, 79-6335
- Carcinogenic, Mutagenic Activity
- Bioassays, Review, 79-6048
- Hepatoma
- Aniline, *N*-Methyl-*p*-(phenylazo)-79-6246
- Aniline, *N,N*-Methyl-*p*-(phenylazo)-Hydroxy-, 79-6246
- Liver Neoplasms
- Carcinogenic Potential, Review 79-6047
- Mutagens
- Soot Extract, 79-6326

Barbituric Acid, 5-Ethyl-5-phenyl- (cont'd)
Sodium Salt
Benzene, (Epoxyethyl)-
Mutagenic Activity, 79-6248

BCG

Leukemia L1210
Immune Response, 79-6478
Leukemia, Myeloblastic
Immunologic Technics, 79-6476

Benz(a)anthracene

Ames Test
Dihydrodiol Metabolites, 79-6293
Aryl Hydrocarbon Hydroxylases
Hepatocytes, Hamster, 79-6288
B-Lymphocytes, 79-6296, 79-6313
Diol Epoxides
Carcinogenic Metabolite, Review
79-6015
DNA, Binding, Review, 79-6014
DNA, Binding
Skin, Mouse, 79-6293
Epoxide Hydratases
Hepatocytes, Hamster, 79-6288
Microsomes, Liver
Carcinogenic Metabolite, Review
79-6017

Benz(a)anthracene, 7-Bromomethyl-

Chromatids
Chromosome Aberrations, 79-6319
Mutagenic Activity
Hamster V70 Cells, 79-6336
Mutation
Azaguanine Resistance, 79-6319

Benz(a)anthracene-7-carboxaldehyde, 12-Methyl-

Light
Photooxidation Product, 79-6290

Benz(a)anthracene-12-carboxaldehyde, 7-Methyl-

Light
Photooxidation Product, 79-6290

Benz(a)anthracene, 3,4-Dihydro-3,4-dihydroxy-7,12-dimethyl-

Skin Neoplasms
Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-7,12-dimethyl-, 79-6309
12-O-Tetradecanoylphorbol-13-acetate
79-6309

Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-7,12-dimethyl-

Skin Neoplasms
Benz(a)anthracene, 3,4-Dihydro-3,4-dihydroxy-7,12-dimethyl-, 79-6309

Benz(a)anthracene, 7,12-Dimethyl-

Ames Test
Dihydrodiol Metabolites, 79-6293
Aryl Hydrocarbon Hydroxylases
Enzyme Inhibition, 79-6313
7,8-Benzoflavone
DNA, Binding, 79-6291

Caffeine
DNA, Binding, 79-6294
Cell Transformation, Neoplastic
Clone Cells, 79-6292

Embryo, Feline, 79-6292
Trachea, Rat, 79-6276

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
DNA, Binding, 79-6327

Dibutyl Cyclic AMP
DNA, Binding, 79-6294

Dietary Fats
Microsomes, Liver, 79-6301

Dihydrodiol Metabolites
Skin, Mouse, 79-6289

Diol Epoxides
DNA, Binding, Review, 79-6014

DNA, Binding
Protease Inhibitors, 79-6291

Protein Synthesis, 79-6291
Skin, Mouse, 79-6293

Ear Neoplasms
4-Stilbenamine, *N,N*-Dimethyl-, 79-6302

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)

Fibrosarcoma
Radiation, Ionizing, 79-6363
Transplantation, Homologous, 79-6297
Transplantation Immunology, 79-6497
Glucosephosphate Dehydrogenase
Zymbal Gland, Rat, 79-6302
Lactate Dehydrogenase
Zymbal Gland, Rat, 79-6302
Leukemia, Lymphocytic
Phorbol, 79-6299

Light
Photooxidation Product, 79-6290
T-Lymphocytes
Lymphocyte Transformation, Review
79-6078

Malate Dehydrogenase
Zymbal Gland, Rat, 79-6302

Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6299

Dietary Carbohydrates, 79-6300
Dietary Fats, 79-6301, 79-6516

Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-6301

Progesterone, 79-6345
Receptors, Hormone, 79-6346

Microsomes, Liver
Dihydrodiol Metabolites, 79-6289

Mouth Neoplasms
Benzene, 1-Chloro-2,4-dinitro-, 79-6298

Oocytes
Toxicity, Mouse, 79-6314

Phenol, (1,1-Dimethylethyl)-4-methoxy-
Ames Test, 79-6301

DNA, Binding, 79-6291
Microsomes, Liver, 79-6301

Phorbol
Co-carcinogenic Effect, 79-6299

Phosphatidylcholines
Biological Membranes, 79-6317

Photoelectric Properties
Biological Membranes, 79-6317

Poly A-U
Immune Response, Mouse, 79-6295

Polylysine
Biological Membranes, 79-6317

Sebaceous Gland Neoplasms
Carcinoma, 79-6302

Carcinoma, Epidermoid, 79-6302
Oxidoreductases, 79-6302

4-Stilbenamine, *N,N*-Dimethyl-
79-6302

Skin Neoplasms
Benzo(a)pyrene, 79-6327

Carcinogenic Metabolite, 79-6309
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
79-6327

Papilloma, 79-6295
Poly A-U, 79-6295

Transplantation, Homologous, 79-6297
Succinate Dehydrogenase

Zymbal Gland, Rat, 79-6302
Theophylline

DNA, Binding, 79-6294

Benz(a)anthracene-7,12-dione

Light
Photooxidation Product, 79-6290

Benz(a)anthracene-7-methanol, 12-Methyl-

Ascorbic Acid
Oxidation Products, 79-6289

Dihydrodiol Metabolites
Skin, Mouse, 79-6289

Light
Photooxidation Product, 79-6290

Microsomes, Liver
Dihydrodiol Metabolites, 79-6289

Sulfuric Acid, Iron Salt
Oxidation Products, 79-6289

Benz(a)anthracene-12-methanol, 7-Methyl-

Dihydrodiol Metabolites
Skin, Mouse, 79-6289

Light
Photooxidation Product, 79-6290

Benz(a)anthracene, 7-Methyl-

Ames Test
Dihydrodiol Metabolites, 79-6293
Diol Epoxides
DNA, Binding, Review, 79-6014
DNA, Binding
Skin, Mouse, 79-6293

Benzamide, *p*-Formyl-*N*-isopropyl-

p-Tolamide, *N*-Isopropyl- α -(2-methylhydrazino)-
Microsomes, Liver, 79-6244

Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-

Antibody Specificity
Carcinogenic Metabolite, 79-6237

Arginase
Liver, Rat, 79-6236

Liver
Binding, 79-6237

Nucleic Acids
Hepatocarcinogenesis, 79-6236

Ornithine Carbamoyltransferase
Liver, Rat, 79-6236

Ornithine Decarboxylase
Liver, Rat, 79-6236

Polyamines
Hepatocarcinogenesis, 79-6236

Benzenamine, 2-Methyl-4-((2-methylphenyl)azo)-

Hepatoma
Alpha Fetoproteins, 79-6234

Glutamyl Transpeptidase, 79-6234

Benzene

Chromosome Aberrations
Mutagenic Activity, Review, 79-6004

Solvents
Chromosome Aberrations, 79-6238

Benzene, 4-Allyl-1,2-(methylenedioxy)-

Nucleic Acids
Mutagenic, Carcinogenic Metabolite,
Review, 79-6020

Benzene, 1-Chloro-2,4-dinitro-

Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6298

Hypersensitivity, Delayed, 79-6298

Benzene, (Epoxyethyl)-

Ames Test
S9 Fraction, 79-6157

Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
Mutagenic Activity, 79-6248

Drosophila melanogaster
Mutagenic Activity, 79-6248

Propane, 1,2-Epoxy-3,3,3-trichloro-
Mutagenic Activity, 79-6248

Benzene, Hexachloro-

Porphyria
Hepatocarcinogenesis, Review
79-6005

1,3-Benzenediamine, 4-Methoxy-

Ames Test
Mutagenic Metabolite, 79-6167

S9 Fraction, Liver, Kidney, 79-6235
Cholanthrene, 3-Methyl-

Aryl Hydrocarbon Hydroxylases
79-6235

Mutagenic Activity, 79-6235
Microsomes, Liver

Mutagenic Metabolite, 79-6167

1,3-Benzenediamine, 4-Methoxy-, Sulfate

Mutagenic Activity
Germ Cells, Rat, 79-6213

1,2,4-Benzenetriol, 5-(2-Aminoethyl)-

Prostatic Neoplasms
Carcinoma, Epidermoid, 79-6307

Benzidine

Bladder Neoplasms
Occupational Hazard, 79-6011

Benzidine (cont'd)
 Erythrocytes
 Micronucleus Test, 79-6260
 Mutagenic Activity, 79-6260

Benzidine, 3,3'-Dimethyl-
 Erythrocytes
 Micronucleus Test, 79-6260
 Mutagenic Activity, 79-6260

1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 Benzoic Acid, 4-(Aminosulfonyl)-
 Metabolism, Rat, 79-6253
 Bladder Neoplasms
 Carcinogenic Activity, Review
 79-6061
 Cholanthrene, 3-Methyl-
 Metabolism, Rat, 79-6253
 Environmental Hazard
 Risk Factors, 79-6578
 Food Additives
 Carcinogenic Potential, Review
 79-6060
 Production Method
 Mutagenic Activity, 79-6252
Saccharomyces cerevisiae
 Mutagenic Activity, 79-6252

Benzo(a)pyren-9-ol
 Cells, Cultured
 Metabolism, 79-6332

Benzo(a)pyrene
 Ames Test
 Dihydrodiol Metabolites, 79-6293
 Hepatocytes, 79-6323
 Soot Extract, 79-6326
 Aryl Hydrocarbon Hydroxylases
 Cells, Cultured, 79-6328
 Cytochrome P-450, 79-6318
 DNA, Binding, 79-6318
 B-Lymphocytes, 79-6313
 Ascorbic Acid
 Dihydrodiol Metabolites, 79-6333
 7,8-Benzoflavone
 Metabolism, 79-6322
 Carcinogenic Metabolite
 Genetics, Mouse, 79-6318
 Cell Transformation, Neoplastic
 Brain, Mouse, 79-6320, 79-6321
 Cells, Cultured
 Metabolism, 79-6332
 Cholanthrene, 3-Methyl-
 Metabolism, 79-6322
 Cholesterol, 14-Methylhexadecanoate
 Liver, Rat, 79-6338
 Chromatids
 Chromosome Aberrations, 79-6319
 Dibenzop-dioxin, 2,3,7,8-Tetrachloro-
 DNA, Binding, 79-6327
 Diol Epoxides
 Carcinogenic Metabolite, Review
 79-6015
 DNA, Binding, Review, 79-6014
 DNA, Binding
 Skin, Mouse, 79-6293
 Epoxide Hydratases
 Mutagenic Metabolite, 79-6329
 Esophagus
 DNA Adducts, 79-6315
 Fibrosarcoma
 Genetics, Mouse, 79-6318
 Microsomes, Liver, 79-6318
 Genetics, Mouse
 DNA, Binding, 79-6318
 Glucuronidase
 Quinone Metabolites, 79-6325
 Glutathione
 Mutagenic Metabolite, 79-6323
 Guanine
 DNA Adducts, 79-6324
 Harman
 Co-carcinogenic Effect, Review
 79-6016
 Lung Neoplasms
 Metabolism, 79-6331
 B-Lymphocytes
 Carcinogenic Metabolite, 79-6296

Benzo(a)pyrene (cont'd)
 Maleic Acid, Diethyl Ester
 Lung, Binding, 79-6322
 Microsomes, Liver
 Ames Test, 79-6318
 DNA Adducts, 79-6335
 Enzyme Activation, 79-6318
 Mutation
 Azaguanine Resistance, 79-6319
 Nerve Tissue Proteins
 Astrocytes, 79-6321
 Cell Transformation, Neoplastic
 79-6321
 Neuroglia
 Ultrastructural Study, 79-6320
 Nicotine
 Lung, Binding, 79-6322
 Norharman
 Co-carcinogenic Effect, Review
 79-6016
 Nucleosides
 Diol Epoxide, 79-6324
 Oocytes
 Toxicity, Mouse, 79-6314
 Oxidation Products
 Dihydrodiol Metabolites, 79-6333
 Oxidoreductases
 Mutagenic Metabolite, 79-6329
 Phosphatidylcholines
 Biological Membranes, 79-6317
 Polylysine
 Biological Membranes, 79-6317
 Propane, 1,2-Epoxy-3,3,3-trichloro-
 Metabolism, 79-6322
 Quinone Metabolites
 Trachea, Hamster, 79-6325
 Skin Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6327
 Smoke Condensate
 Mutagenic Activity, Review, 79-6016
 Soft Tissue Neoplasms
 Cholesterol, 14-Methylhexadecanoate
 79-6338
trans-Stilbene Oxide
 Ames Test, 79-6316
 Carcinogenic Metabolite, 79-6316
 Sulfuric Acid, Iron Salt
 Dihydrodiol Metabolites, 79-6333
 UDP Glucuronosyltransferase
 Cells, Cultured, 79-6328

Benzo(a)pyrene, 4,5-Dihydro-4,5-
 dihydroxy-
 Ascorbic Acid
 Dihydrodiol Metabolites, 79-6333
 Cells, Cultured
 Metabolism, 79-6332

Benzo(a)pyrene, 7,8-Dihydro-7,8-
 dihydroxy-
 Ascorbic Acid
 Dihydrodiol Metabolites, 79-6333
 Cells, Cultured
 Carcinogenic Metabolite, 79-6328
 79-6332
 Esophagus
 Carcinogenic Metabolite, 79-6315
 Lung Neoplasms
 Adenoma, 79-6017
 Carcinogenic Metabolite, Review
 79-6017
 Lymphoma
 Carcinogenic Metabolite, Review
 79-6017

Benzo(a)pyrene, 9,10-Dihydro-9,10-
 dihydroxy-
 Ascorbic Acid
 Dihydrodiol Metabolites, 79-6333
 Cells, Cultured
 Carcinogenic Metabolite, 79-6328
 Metabolism, 79-6332
 Metabolism
 Organ Culture, 79-6331

Benzo(a)pyrene, 11,12-Dihydro-11,12-
 dihydroxy-
 Ascorbic Acid
 Dihydrodiol Metabolites, 79-6333

Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
 7,8,9,10-tetrahydro-
 Ames Test
 DNA Adducts, 79-6335
 Aroclor 1254
 Ames Test, 79-6335
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Ames Test, 79-6335
 Cholanthrene, 3-Methyl-
 Ames Test, 79-6335
 Chromatids
 Chromosome Aberrations, 79-6319
 Microsomes, Liver
 Carcinogenic Metabolite, Review
 79-6017
 Mutagenic Activity
 DNA, Binding, 79-6336
 Hamster V79 Cells, 79-6336
 Mutation
 Azaguanine Resistance, 79-6319
 Oxidoreductases
 Metabolism, 79-6329
 Skin Neoplasms
 Nucleoside Adducts, 79-6327

Benzo(a)pyrene 4,5-Oxide
 Ames Test
 Enantiomers, 79-6334
 Chromatids
 Chromosome Aberrations, 79-6319
 Microsomes, Liver
 Mutagenic Metabolite, 79-6017
 Mutagenic Activity
 Hamster V79 Cells, 79-6334, 79-6336
 Mutation
 Azaguanine Resistance, 79-6319
trans-Stilbene Oxide
 Epoxide Hydratases, 79-6316

Benzo(a)pyrene, 7,8,9,10-Tetrahydro-
 7,8,9,10-tetrahydroxy-
 Esophagus
 DNA Adducts, 79-6315

Benzo(a)pyrene, 7,8,9-Trihydroxy-
 7,8,9,10,10-pentahydro-
 Metabolism
 Organ Culture, 79-6331

Benzo(e)pyrene
 Cells, Cultured
 Metabolism, 79-6332

5,6-Benzoflavone
 Dibenz(a,h)anthracene
 Aryl Hydrocarbon Hydroxylases
 79-6313

7,8-Benzoflavone
 Acetamide, *N*-Fluoren-2-yl-
 Ames Test, 79-6166
 Benz(a)anthracene, 7,12-Dimethyl-
 DNA, Binding, 79-6291
 Benzo(a)pyrene
 Metabolism, 79-6322
 Dibenz(a,h)anthracene
 Aryl Hydrocarbon Hydroxylases
 79-6313
 4,4'-Stilbenediol, α,α' -Diethyl-
 Chromatids, 79-6341

Benzoic Acid, 4-(Aminosulfonyl)-
 1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 Metabolism, Rat, 79-6253

Benzoic Acid, 2,3,6-Trichloro-
 Food Contamination
 Carcinogenic Potential, Review
 79-6098

Benzylamine, *N*-Methyl-*N*-nitroso-
 Esophageal Neoplasms
 Animal Model, Rat, 79-6233
 Carcinoma, Epidermoid, 79-6233
 Carcinoma, Papillary, 79-6233

Benzylamine, N-Methyl-N-nitroso- (cont'd)
Mycotoxins, 79-6197
Papilloma, 79-6233

Beryllium

Air Pollution
Epidemiology, Review, 79-6054
79-6105
Carrier Proteins
Liver, Rat, 79-6134
Chromatin
Liver, Rat, 79-6134
Nucleoproteins
Binding, 79-6134
Phosphoproteins
Binding, 79-6134

Beta-Glucosidases

Cycasin
Ames Test, 79-6146
Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
Ames Test, 79-6146
Methanol, (Methyl-*ONN*-azoxy)-
Ames Test, 79-6146

Bile Acids and Salts

5 β -Cholan-24-oic Acid, 3 α ,7 α -
Dihydroxy-
Metabolism, Rat, 79-6208
Colonic Neoplasms
5 β -Cholan-24-oic Acid, 3 α ,7 α -
Dihydroxy-, 79-6208

Bile Duct Neoplasms

Cholangioma
Morpholine, *N*-Nitroso-, 79-6215
Coumarin
Metabolism, Review, 79-6066

4-Biphenylamine

Smoke Condensate
Aromatic Amines, 79-6241

3,3'-Biphenyldicarboxylic Acid, 4,4'-

Diamino-
Sarcoma
Carcinogenic Potential, Rat, 79-6251
Urogenital Neoplasms
Carcinogenic Potential, Rat, 79-6251

4,4'-Bipyridinium, 1,1'-Dimethyl-, Di-

chloride
Lactic Acid
Lung, Mouse, 79-6187

Black Pepper

see *Piper nigrum*

Bladder Diseases

Cystitis
Cyclophosphamide, 79-6580

Bladder Neoplasms

Alkaline Phosphatase
Cell Division, Review, 79-6095
Benzidine
Occupational Hazard, 79-6011
1,2-Benzisothiazolin-3-one, 1,1-Dioxide
Carcinogenic Activity, Review
79-6061
Carcinoma, Transitional Cell
Cyclophosphamide, 79-6580
Glucocorticoids
Receptors, Hormone, Review, 79-6095
Hyperplasia
Cell Division, Review, 79-6095
Metaplasia
Cell Membrane, 79-6203
2-Naphthylamine
Occupational Hazard, 79-6011
Occupational Hazard
Epidemiology, Review, 79-6011
Opium
Epidemiology, Iran, 79-6581
Smoking
Epidemiology, Iran, 79-6581
Tars
Smoking, 79-6584
Urea, Methyl Nitroso-

Bladder Neoplasms (cont'd)

Cell Membrane, 79-6203
Precancerous Conditions, 79-6203

Blood Proteins

Aniline, *N,N*-Dimethyl-*p*-phenylazo-
Binding, 79-6247
4-Stilbenamine, *N,N*-Dimethyl-
Metabolism, Rat, 79-6340

Bloom's Syndrome

see Dwarfism

Bone and Bones

Americium
Half-Life, 79-6375

Bone Neoplasms

Sarcoma, Ewing's
Diagnosis and Prognosis, 79-6562
Neoplasm Metastasis, 79-6562

Bracken Fern

Digestive System Neoplasms
Epidemiology, Review, 79-6022
Mycotoxins
Epidemiology, Review, 79-6022

Brain Neoplasms

Acrylonitrile
Carcinogenic Activity, Rat, 79-6181
Carcinoma, Bronchiolar
Neoplasm Metastasis, 79-6532
Encephalitis
Virus, Herpes Simplex 2, 79-6532
Ependymoma
Urea, Nitroso-, 79-6201
Glioma
Urea, Nitroso-, 79-6201
Melanoma
Neoplasm Metastasis, 79-6534
Meningioma
Radiation, Ionizing, 79-6529
Oligodendroglioma
Urea, Nitroso-, 79-6201

Breast Neoplasms

Age Factors
Epidemiology, Review, 79-6117
Alpha Particles
Theoretical Model, Review, 79-6070
Androgens
Receptors, Hormone, 79-6349
Carcinoma
Epidemiology, Surinam, 79-6572
Histological Study, 79-6572
Receptors, Hormone, 79-6349
Contraceptives, Oral
Epidemiology, Review, 79-6116
Diet
Epidemiology, 79-6571
Milk, Eggs, 79-6571
Estradiol
Genes, Embryonic, Review, 79-6030
Estrogens
Dietary Fats, Review, 79-6029
Receptors, Hormone, 79-6346
79-6347, 79-6349
Gastritis
Hemorrhage, 79-6550
Genetics
Epidemiology, Review, 79-6117
Histocytes
Lymph Nodes, 79-6548
Neoplasm Metastasis, 79-6548
Intestinal Neoplasms
Epidemiology, 79-6558
Lymph Nodes
Immune Response, 79-6549
T-Lymphocytes, 79-6549
Neoplasm Metastasis, 79-6549
Neoplasms, Multiple Primary
Epidemiology, Review, 79-6117
Polish Migrants
England, Wales, 79-6557
Progesterone
Receptors, Hormone, 79-6347
79-6349
Prolactin

Breast Neoplasms (cont'd)

Dietary Fats, Review, 79-6029
Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester
Epidemiology, 79-6155
Receptors, Hormone
Isolation and Characterization
79-6346
Prognosis, 79-6347
Retinol
Serum Levels, 79-6339
Zinc, 79-6339

Burkitt's Lymphoma

Abdominal Neoplasms
Nonendemic Disease, 79-6524
Chromosome Aberrations
Chromosomes, Human, 6-12, 79-6487
Chromosome Abnormalities
Diagnosis and Prognosis, 79-6524
Chromosomes, Human, 13-15
Chromosome Abnormalities, Review
79-6127
Eye Neoplasms
Histopathological Study, 79-6554
Immunoblastic Lymphadenopathy
Case Report, 79-6487
Jaw Neoplasms
Nonendemic Disease, 79-6524
Lymph Nodes
Histological Study, 79-6523
Malaria
Epidemiology, Review, 79-6127
Ovarian Neoplasms
Nonendemic Disease, 79-6524
Virus, Epstein-Barr
Antibodies, Viral, 79-6524
Chromosome Aberrations, Review
79-6078
Epidemiology, Review, 79-6127

1,3-Butadiene, 1-Chloro-

Drosophila melanogaster
Mutagenic Activity, 79-6158

1,3-Butadiene, 2-Chloro-

Drosophila melanogaster
Mutagenic Activity, 79-6158
Lung Neoplasms
Carcinogenic Potential, Review
79-6050
Sarcoma 180, Crocker
Immune Response, Review, 79-6050
Skin Neoplasms
Carcinogenic Potential, Review
79-6050

Butane, 1,4-Dichloro-2,3-epoxy-

Drosophila melanogaster
Mutagenic Activity, 79-6158

Butane, 1,2-Epoxy-

Ames Test
S9 Fraction, 79-6157

1,4-Butanediol, Dimethylsulfonate

Leukemia, Myeloblastic
Drug Therapy, 79-6009

2,3-Butanedione

Ames Test
Mutagenic Activity, 79-6160

1-Butanol, 2,2'-(1,2-Ethanediylidimino)bis-

Nitroso Compounds
Precursors, Review, 79-6057

2-Butanone, 3-((3-

Methylbutyl)nitrosamino)-
Esophageal Neoplasms
Food Contamination, 79-6197
Mycotoxins, 79-6197

2-Butene, 1,4-Dichloro-

Drosophila melanogaster
Mutagenic Activity, 79-6158

Butyric Acid

Cell Transformation, Neoplastic
Peptides, 79-6599

Butyric Acid, 2-Amino-4-(ethylthio)-
Sarcoma, Mast Cell
DNA, Methylation, 79-6156
Nucleotide Sequence, 79-6156

Cadmium
Water Pollution
Risk Factors, Review, 79-6109

Cadmium Chloride
Chromosome Aberrations
Metaphase, 79-6135
Oocytes, Hamster, 79-6135

Caffeine
Benz(a)anthracene, 7,12-Dimethyl-
DNA, Binding, 79-6294
Carbamic Acid, Ethyl Ester
Mutagenic Activity, 79-6198
Lupus Erythematosus, Systemic
DNA Repair, 79-6358
Mitomycin C
Chromatids, 79-6226
Chromosome Aberrations, 79-6226
Quinoline, 4-Nitro-, 1-Oxide
DNA Repair, 79-6358
Ultraviolet Rays
DNA Repair, 79-6358
Xeroderma Pigmentosum
DNA Repair, 79-6357

Calcium
Cell Division
Fibroblasts, 79-6385
Glioma
Acetic Acid, (Ethylenebis(oxy-
thylene)nitro)tetra-, 79-6164
Adenosine Cyclic 3',5' Monophos-
phate, 79-6164
Adrenergic Beta Receptor Agonists
79-6164

**Carbamic Acid, Diisopropylthio-, S-(2,3-
Dichloroallyl) Ester**
Acrolein, 2-Chloro-
Mutagenic Metabolite, 79-6056
Microsomes, Liver
Mutagenic Metabolite, 79-6056
Mutagenic Metabolite
Sulfoxide Derivatives, Review
79-6056

**Carbamic Acid, Diisopropylthio-, S-(2,3,3-
Trichloroallyl) Ester**
Mutagenic Metabolite
Sulfoxide Derivatives, Review
79-6056

Carbamic Acid, Ethyl Ester
Caffeine
Mutagenic Activity, 79-6198
Drosophila melanogaster
Mutagenic Activity, 79-6198
Sex Chromosomes, 79-6198
Lung Neoplasms
p-Cresol, 2,6-Di-tert-butyl-, 79-6110
Lactic Acid, 79-6187
Phosphotransferases, ATP, 79-6187
Nucleic Acids
Mutagenic, Carcinogenic Metabolite,
Review, 79-6020

**Carbamic Acid, N-Methyl-N-nitroso-, Eth-
yl Ester**
Nucleic Acids
Lung, Rat, 79-6207
Pulmonary Surfactant
Lung, Rat, 79-6207

Carbamic Acid, Vinyl Ester
Nucleic Acids
Mutagenic, Carcinogenic Metabolite,
Review, 79-6020

Carbamoyl Chloride, Dimethyl-
Occupational Hazard
Carcinogenic Potential, Review
79-6113

Carbon Monoxide
Air Pollution
Toxicity, Review, 79-6105

Carbon Tetrachloride
Alanine Aminotransferase
Serum Levels, 79-6147
Cysteine
Metabolism, 79-6149
Diet
Hepatocarcinogenesis, 79-6259
Glucosephosphatase
Liver, Rat, 79-6147
Glutathione
Metabolism, 79-6149
Hyperplasia
Pulmonary Alveoli, 79-6207
Isopropyl Alcohol
Hepatotoxicity, 79-6147
Methanol
Hepatotoxicity, 79-6147
Nucleic Acid Replication
Lung, Rat, 79-6207
Phosgene
Liver, Rat, 79-6149
Pulmonary Surfactant
Lung, Rat, 79-6207
Triglycerides
Liver, Rat, 79-6147

Carbonyl Chloride
see Phosgene

Carcinoembryonic Antigen
Gastritis
Gastric Mucosa, 79-6512
Stomach Neoplasms
Precancerous Conditions, 79-6512

Carcinogen, Chemical
Air Pollution
Bioassays, 79-6263
Ames Test
Bioassays, Review, 79-6048
Mutagenic Activity, 79-6169
Cell Transformation, Neoplastic
Cells, Cultured, Review, 79-6036
Chlorophyll
Ames Test, 79-6131
Chromosome Aberrations
Bioassays, Review, 79-6048
Risk Evaluation, Review, 79-6035
Diet
Metabolism, Review, 79-6040
DNA, Binding
Bioassay, Review, 79-6021
DNA Repair
Chromatin, Review, 79-6063
Toxicity, Review, 79-6034
Environmental Hazard
Thresholds, Review, 79-6045, 79-6108
Fetal Globulins
Immune Response, Review, 79-6039
Hair Dyes
Risk Factors, Review, 79-6062
Hepatoma
Alpha Fetoproteins, Review, 79-6038
Chromosomal Proteins, Non-Histone,
Review, 79-6038
Leukemia
Dietary Proteins, Review, 79-6041
Lung Neoplasms
Enzyme Activation, Review, 79-6102
Metabolism
DNA Adducts, Review, 79-6008
Microsomes, Liver
Ames Test, 79-6242
Neoplasms, Experimental
Dose-Response Study, Review
79-6032, 79-6058
Hamster, Review, 79-6044
Occupational Hazard
Thresholds, 79-6106
Oncogenic Viruses
Virus Activation, Review, 79-6073
Quasi-Valence Number
Identification and Classification
79-6128

Carcinogen, Chemical (cont'd)

Risk Factors
Mathematical Model, Review, 79-6032
Sarcoma
Fetal Globulins, Review, 79-6081
Structure-Activity Relationship
Ames Test, Review, 79-6023
Transplantation Immunology
Fetal Globulins, Review, 79-6081
Ultraviolet Rays
Quasi-Valence Number, 79-6128
Virus, Adeno
Focus Formation Assay, 79-6036
Virus, Rauscher Murine Leukemia
Focus Formation Assay, 79-6036

Carcinogen, Environmental

Air Pollution
Epidemiology, Review, 79-6104
Ames Test
Mutagenic Activity, Review, 79-6016
Cell Transformation, Neoplastic
Dose-Response Relationship, Review
79-6016
Dose-Response Relationship
Mathematical Model, 79-6033
Ethylene, Chloro-
Experimental Toxicology, Review
79-6104
Mycotoxins
Epidemiology, Review, 79-6111
Experimental Toxicology, Review
79-6104
Neoplasms, Experimental
Risk Evaluation, Review, 79-6043
Nitrosamines
Epidemiology, Review, 79-6111
Polycyclic Hydrocarbons
Epidemiology, Review, 79-6111
Radiation, Ionizing
Epidemiology, Review, 79-6111
4,4'-Stilbenediol, α,α' -Diethyl-
Experimental Toxicology, Review
79-6104
Sulfide, Bis(2-chloroethyl)-
Experimental Toxicology, Review
79-6104

Carcinoid Tumor

Adenomatosis, Familial Endocrine
Genetics, Review, 79-6093
Intestinal Neoplasms
Epidemiology, India, 79-6582
Stomach Neoplasms
Gastrin, 79-6539
Immunohistochemical Study, Masto-
mys, 79-6539
Serotonin, 79-6539
Somatotropin Release Inhibiting Hor-
mone, 79-6539

Carcinoma

Breast Neoplasms
Epidemiology, Surinam, 79-6572
Histological Study, 79-6572
Receptors, Hormone, 79-6349
Cervix Neoplasms
Epidemiology, Review, 79-6118
Precancerous Conditions, Review
79-6118
Esophageal Neoplasms
Alcoholic Beverages, 79-6566
Smoking, 79-6566
Laryngeal Neoplasms
Smoking, 79-6284
Mammary Neoplasms, Experimental
Adenosine, Methyl Nitroso-, 79-6232
Mouth Neoplasms
Leukoplakia, Oral, 79-6531
Pancreatic Neoplasms
Propionic Acid, 2-(p-Chlorophenoxy)-
2-methyl-, Ethyl Ester, 79-6153
79-6154
Serine, Diazoacetate (Ester), 79-6508
Transplantation, Heterologous
79-6508
Sebaceous Gland Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-

Carcinoma (cont'd)
Benz(a)anthracene, 7,12-Dimethyl-
79-6302
Stomach Neoplasms
Gastrectomy, 79-6512
Aniline, *N,N*-Methyl-*p*-(phenylazo)-,
Hydroxy-, 79-6246
Thyroid Neoplasms
Radiation, Ionizing, 79-6369
Urea, 1-(2-Chloroethyl)-3-(2-
hydroxyethyl)-1-nitroso-
Drug Therapy, 79-6211

Carcinoma, Basal Cell
Eye Neoplasms
Epidemiology, Sudan, 79-6554
Leukemia, Lymphocytic
Case Report, 79-6473

Carcinoma, Bronchiolar
Brain Neoplasms
Neoplasm Metastasis, 79-6532

Carcinoma, Ductal
Pancreatic Neoplasms
Animal Model, Nude Mouse, 79-6508
Nitrosamines, 79-6508
Transplantation, Heterologous
79-6508

Carcinoma, Ehrlich Tumor
Energy Metabolism
Phenotype, 79-6536
Glucose
Karyotyping, 79-6536
Succinic Acid, Disodium Salt
Karyotyping, 79-6536
Trypan Blue
Antibody-Dependent Cell Cytotoxicity
79-6488
Immunity, Cellular, 79-6488

Carcinoma, Epidermoid
Arsenious Acid, Potassium Salt
Case Report, 79-6132
Cervix Neoplasms
Virus, Herpes Simplex 2, 79-6426
Esophageal Neoplasms
Benzylamine, *N*-Methyl-*N*-nitroso-
79-6233
Epidemiology, Israel, 79-6566
Immunity, Cellular, 79-6511
Pentylamine, *N*-Methyl-*N*-nitroso-
79-6214
Eye Neoplasms
Epidemiology, Sudan, 79-6554
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Cells, Cultured, 79-6220
Hypercalcemia
Arsenious Acid, Potassium Salt
79-6132
Leukemia, Lymphocytic
Case Report, 79-6473
Leukemia, Myeloblastic
Case Report, 79-6520
Lung Neoplasms
Bronchopulmonary Sequestration
79-6537
Case Report, 79-6537
Lymphangiosarcoma
Radiotherapy, 79-6370
Lymphosarcoma
Case Report, 79-6473
Morpholine, *N*-Nitroso-
Carcinogenic Activity, Rat, 79-6215
Nose Neoplasms
Pentylamine, *N*-Methyl-*N*-nitroso-
79-6214
Prostatic Neoplasms
1,2,4-Benzenetriol, 5-(2-Aminoethyl)-
79-6307
Cholanthrene, 3-Methyl-, 79-6307
Testosterone, 79-6307
Sebaceous Gland Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6302
Skin Neoplasms
Chrysene, 6-Fluoro-5-methyl-, 79-6305

Carcinoma, Epidermoid (cont'd)
Leukemia, Myeloblastic, 79-6520
Vaginal Neoplasms
Epidemiology, Review, 79-6125
Neoplasm Metastasis, Review, 79-6125
Vulvar Neoplasms
Epidemiology, Review, 79-6125

Carcinoma In Situ
Cervix Neoplasms
Epidemiology, Review, 79-6118
Imidazole-1-ethanol, 2-Methyl-5-nitro-
79-6217
Trichomonas vaginalis, 79-6217
Intestinal Neoplasms
Hydrazine, 1,2-Dimethyl-, 79-6175
Precancerous Conditions, 79-6175
Stomach Neoplasms
Classification, Review, 79-6094

Carcinoma, Papillary
Esophageal Neoplasms
Benzylamine, *N*-Methyl-*N*-nitroso-
79-6233
Thyroid Neoplasms
Radiation, Ionizing, 79-6368
Urogenital Neoplasms
Propionic Acid, 2-(*p*-Chlorophenoxy)-
2-methyl-, Ethyl Ester, 79-6153

Carcinoma, Transitional Cell
Bladder Neoplasms
Cyclophosphamide, 79-6580

Carcinoma 256, Walker
Cholest-5-en-3 β -ol, Hexadecanoate
Metabolism, 79-6338
Cholesterol, 14-Methylhexadecanoate
Metabolism, 79-6338
Interferon
Growth, 79-6463

Carcinosarcoma
Acridine, 3,6-Diamino-
Light, 79-6287
Mammary Neoplasms, Experimental
Ultraviolet Rays, 79-6287
Psoralen, 8-Methoxy-
Light, 79-6287

Carotid Body Tumor
Neoplasms, Multiple Primary
Astrocytoma, 79-6376

Carrier Proteins
Beryllium
Liver, Rat, 79-6134
Colonic Neoplasms
DNA, 79-6177

Caseln
Amyloid
Isolation and Characterization, Mouse
79-6492

Catalase
Copper
Feces, 79-6140

Catecholamines
Prostatic Neoplasms
Cholanthrene, 3-Methyl-, 79-6307

Cell Aggregation
Lymphoma
Lactose, 79-6593
Sodium Azide, 79-6593
Sodium Fluoride, 79-6593
Vinblastine Sulfate
Cytochalasin B, 79-6593

Cell Differentiation
Plasmacytoma
T-Lymphocytes, 79-6489
Teratoid Tumor
Virus, AKR Murine Leukemia
79-6406
Virus, SV40, 79-6075
12-*O*-Tetradecanoylphorbol-13-acetate
Fibroblasts, 79-6271
Muscles, 79-6271

Cell Differentiation (cont'd)
Myofibrils, 79-6271

Cell Division
Aflatoxin B1
Gene Deletion, Review, 79-6019
Calcium
Fibroblasts, 79-6385
Chromatin
Liver, Rat, 79-6590
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Chromatids, 79-6224
Magnesium
Fibroblasts, 79-6385
Phorbol 12,13-Dibenzate
Ornithine Decarboxylase, 79-6275
Phthalic Acid, Bis(2-butoxyethyl) Ester
Toxicity, Review, 79-6006
Phthalic Acid, Bis(2-ethylhexyl) Ester
Toxicity, Review, 79-6006
Polycyclic Hydrocarbons
Gene Deletion, Review, 79-6019
12-*O*-Tetradecanoylphorbol-13-acetate
Ornithine Decarboxylase, 79-6275
Virus, Polyoma
Hyaluronidase, 79-6435
Virus, Rous Sarcoma
Cations, Divalent, 79-6385

Cell Membrane
Bladder Neoplasms
Metaplasia, 79-6203
Urea, Methyl Nitroso-, 79-6203
Leukemia
Histocompatibility Antigens, 79-6477
Phorbol Esters
Glycoproteins, 79-6267
Trypan Blue
Complement, 79-6488
Virus, Abelson Murine Leukemia
Viral Proteins, 79-6403
Virus, Friend Spleen Focus-Forming
Antigens, 79-6407
Virus, Murine Sarcoma
Sialic Acid, 79-6538
Virus, Rous Sarcoma
Antigens, 79-6388
Chondroitin, 79-6389

Cell Transformation, Neoplastic
Adenolymphoma
Case Report, 79-6519
Aniline, *p*-(Phenylazo)-
Carcinogenic Metabolite, 79-6288
Benz(a)anthracene, 7,12-Dimethyl-
Embryo, Feline, 79-6292
Trachea, Rat, 79-6276
Benzo(a)pyrene
Brain, Mouse, 79-6320, 79-6321
Nerve Tissue Proteins, 79-6321
Butyric Acid
Peptides, 79-6599
Carcinogen, Chemical
Cells, Cultured, Review, 79-6036
Carcinogen, Environmental
Dose-Response Relationship, Review
79-6016
Contact Inhibition
Cells, Cultured, Review, 79-6091
Diethylamine, *N*-Nitroso-
Carcinogenic Metabolite, 79-6288
Cytochalasin B, 79-6195
Tissue Culture, 79-6195
Fibroblasts
Contact Inhibition, 79-6091
Homeostasis, 79-6385
Fluorene, 2,5-Diazido-
Ultraviolet Rays, 79-6139
Fluorene, 2,7-Diazido-
Ultraviolet Rays, 79-6139
Fluorene, 2-Nitro-
Carcinogenic Metabolite, 79-6288
Growth Substances
Horse Serum, 79-6129
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Trachea, Rat, 79-6220
Methanesulfonic Acid, Ethyl Ester
Peptides, 79-6599

Cell Transformation, Neoplastic (cont'd)

- Nitrous Acid, Sodium Salt
- Morpholine, 79-6180
- Radiation, Ionizing
 - Antipain, 79-6361
 - DNA Repair, 79-6361
 - Dose Fractionation, 79-6360
 - Neutrons, 79-6360
 - 12-O-Tetradecanoylphorbol-13-acetate 79-6361
- RNA, Messenger
 - Molecular Biology, Review, 79-6001
- Sarcoma
 - Dose-Response Study, 79-6499
- 12-O-Tetradecanoylphorbol-13-acetate
 - Trachea, Rat, 79-6276
- Virus Adeno 2
 - Peptides, 79-6454
- Virus, Avian Erythroblastosis
 - RNA, Viral, 79-6384
- Virus, Avian Sarcoma
 - Chorioallantoic Membrane, 79-6381
 - Temperature Sensitive Mutants 79-6381
 - Viral Proteins, 79-6382
- Virus, Epstein-Barr
 - Strain Difference, 79-6428
- Virus, Harvey Murine Sarcoma
 - Phosphoproteins, 79-6411
- Virus, Herpes Gorilla
 - B-Lymphocytes, 79-6424
- Virus, Herpes Simplex 1
 - Peptides, 79-6599
- Virus, Kirsten Murine Sarcoma
 - Phosphoproteins, 79-6411
- Virus, Murine Mammary Tumor
 - Virus Rescue, 79-6393
- Virus, Polyoma
 - Cell Cycle Kinetics, 79-6435
 - Deletion Mutants, 79-6433
 - DNA, Viral, 79-6439
 - Peptides, 79-6599
 - Temperature Sensitive Mutants 79-6435, 79-6438
- Virus, Rat Leukemia
 - Immune Serums, 79-6412
- Virus, Rauscher Murine Leukemia
 - RNA Polymerase, 79-6402
- Virus, Rous Sarcoma
 - Antigens, 79-6388
 - Antigens, Viral, 79-6386
 - Chondroitin, 79-6389
 - Fetal Globulins, 79-6388
 - Fibroblasts, 79-6385
 - Glycosaminoglycans, 79-6389
 - Hyaluronic Acid, 79-6389
 - Temperature Sensitive Mutants 79-6387
- Virus, SV40
 - Deletion Mutants, 79-6447
 - Temperature Sensitive Mutants 79-6447
 - Ultraviolet Rays, 79-6356
- Xeroderma Pigmentosum
 - Virus, SV40, 79-6356

Cells, Cultured

- Polychlorobiphenyl Compounds
- Aryl Hydrocarbon Hydroxylases 79-6249

Cerebellar Neoplasms

- Astrocytoma
- Radiation, Ionizing, 79-6376

Cervix Neoplasms

- Carcinoma
 - Epidemiology, Review, 79-6118
 - Precancerous Conditions, Review 79-6118
- Carcinoma, Epidermoid
 - Virus, Herpes Simplex 2, 79-6426
- Carcinoma In Situ
 - Imidazole-1-ethanol, 2-Methyl-5-nitro- 79-6217
 - Trichomonas vaginalis*, 79-6217
- Virus, Herpes Simplex 1
 - Lymphocyte Transformation, 79-6426

Cervix Neoplasms (cont'd)

- Virus, Herpes Simplex 2
 - Lymphocyte Transformation, 79-6426

Chalones

- Ornithine Decarboxylase
- Precancerous Conditions, 79-6275

Chemotaxis

- Leukemia, Lymphoblastic
- Immune Serums, 79-6474
- Inhibitory Factor, 79-6474

Chloral Hydrate

- Cytochrome P-450
- Epoxide Metabolites, 79-6151

Chlordane

- Diet
 - Hepatocarcinogenesis, 79-6259
- Hepatoma
 - Alpha Fetoproteins, 79-6172
- Neoplasm Transplantation, 79-6172

Chloroform

- Diet
 - Hepatocarcinogenesis, 79-6259

Chlorophyll

- Carcinogen, Chemical
 - Ames Test, 79-6131
- Plant Extracts
 - Antimutagenic Activity, 79-6131

Chlorophyllin A

- Salmonella typhimurium*
 - Growth, 79-6131

5 β -Cholan-24-oic Acid, 3 α ,7 α -Dihydroxy-

- Bile Acids and Salts
 - Metabolism, Rat, 79-6208
- Colonic Neoplasms
 - Bile Acids and Salts, 79-6208
- Urea, Methyl Nitroso-, 79-6208

5 β -Cholan-24-oic Acid, 3 α ,12 α -Dihydroxy-

- Colonic Neoplasms
 - Bile Acids and Salts, Review, 79-6051

5 β -Cholan-24-oic Acid, 3 α -Hydroxy-

- Diet
 - Metabolism, 79-6162

5 β -Cholan-24-oic Acid, 3 α -Hydroxy-, 3 α -

- Sulfate
 - Bacteria
 - Metabolism, 79-6162
- Diet
 - Metabolism, 79-6162

Cholangioma

- Alpha 1-Antitrypsin
 - Immunohistochemical Study, 79-6542
- Bile Duct Neoplasms
 - Morpholine, N-Nitroso-, 79-6215
- Hydrocarbons, Chlorinated
 - Histological Study, 79-6259
- Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-
 - Drug Therapy, 79-6211

Cholanthren-2-ol, 3-Methyl-

- Lung Neoplasms
 - Adenoma, 79-6308
- Metabolism
 - Nuclei, Liver, 79-6312
- Skin Neoplasms
 - 12-O-Tetradecanoylphorbol-13-acetate 79-6308

Cholanthren-2-one, 3-Methyl-

- Lung Neoplasms
 - Adenoma, 79-6308
- Skin Neoplasms
 - 12-O-Tetradecanoylphorbol-13-acetate 79-6308

Cholanthrene, 4,5-Dihydro-4,5-dihydroxy-3-

- methyl-
 - Metabolism
 - Nuclei, Liver, 79-6312

Cholanthrene, 9,10-Dihydro-9,10-

- dihydroxy-3-methyl-
 - Metabolism
 - Nuclei, Liver, 79-6312

- Skin Neoplasms
 - 12-O-Tetradecanoylphorbol-13-acetate 79-6309

Cholanthrene, 11,12-Dihydro-11,12-

- dihydroxy-3-methyl-
 - Metabolism
 - Nuclei, Liver, 79-6312

Cholanthrene, 9,10-Dihydro-3-methyl-

- 1,9,10-trihydroxy-
 - Cholanthrene, 3-Methyl-
 - Carcinogenic Metabolite, 79-6308
- Lung Neoplasms
 - Adenoma, 79-6308
- Skin Neoplasms
 - 12-O-Tetradecanoylphorbol-13-acetate 79-6308

Cholanthrene, 3-Methyl-

- Ames Test
 - Dihydrodiol Metabolites, 79-6293
- Aryl Hydrocarbon Hydroxylases
 - Hepatocytes, Hamster, 79-6288
 - B-Lymphocytes, 79-6313
 - Ovary, Mouse, 79-6314
- 1,3-Benzenediamine, 4-Methoxy-
 - Aryl Hydrocarbon Hydroxylases, 79-6235
 - Mutagenic Activity, 79-6235
- 1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 - Metabolism, Rat, 79-6253
- Benzo(a)pyrene
 - Metabolism, 79-6322
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
 - 7,8,9,10-tetrahydro-
 - Ames Test, 79-6335
- Cholanthrene, 9,10-Dihydro-3-methyl-
 - 1,9,10-trihydroxy-
 - Carcinogenic Metabolite, 79-6308
- Diol Epoxides
 - DNA, Binding, Review, 79-6014
- DNA, Binding
 - Skin, Mouse, 79-6293
- Epoxide Hydratases
 - Hepatocytes, Hamster, 79-6288
- Fibrosarcoma
 - Macrophages, 79-6495
 - Membrane Proteins, 79-6596
 - Neoplasm Transplantation, 79-6496
 - Phosphoglycerate Kinase, 79-6306
 - Sex Chromosomes, 79-6306
- Fluoren-2-amine
 - Aryl Hydrocarbon Hydroxylases 79-6235
 - Mutagenic Activity, 79-6235
- Hyperplasia
 - Pulmonary Alveoli, 79-6207
- Lymphoma
 - Histocompatibility Antigens, 79-6484
 - Neoplasm Metastasis, 79-6484
- Metabolism
 - Liver, Rat, 79-6312
- Microsomes, Liver
 - Metabolism, 79-6312
- Mitochondria, Liver
 - Oxidative Phosphorylation, 79-6311
- Nucleic Acid Replication
 - Lung, Rat, 79-6207
- Oocytes
 - Toxicity, Mouse, 79-6314
- D-erythro-Pentose, 2-Deoxy-
 - Oxidative Phosphorylation, 79-6311
- Phosphoglycerate Kinase
 - Phenotype, 79-6306
- Prostatic Neoplasms
 - Carcinoma, Epidermoid, 79-6307
 - Catecholamines, 79-6307
 - Indole-3-acetic Acid, 5-Hydroxy- 79-6307
 - Serotonin, 79-6307
- Pulmonary Surfactant
 - Lung, Rat, 79-6207
- Sarcoma
 - Antigens, Neoplasm, 79-6310

Cholanthrene, 3-Methyl-(cont'd)
 T-Lymphocytes, 79-6502
 Skin Neoplasms
 Carcinogenic Metabolite, 79-6309

Cholest-5-en- β -ol, Hexadecanoate
 Carcinoma 256, Walker
 Metabolism, 79-6338

Cholesterol
 Ames Test
 Autooxidation Products, 79-6337
 Neoplasms
 Epidemiology, Review, 79-6026

Cholesterol, 14-Methylhexadecanoate
 Benzo(a)pyrene
 Liver, Rat, 79-6338
 Carcinoma 256, Walker
 Metabolism, 79-6338
 Hepatoma
 Metabolism, 79-6338
 Soft Tissue Neoplasms
 Benzo(a)pyrene, 79-6338

Choline
 Liver Neoplasms
 Diethylamine, *N*-Nitroso-, 79-6194

Chondroitin
 Virus, Rous Sarcoma
 Cell Membrane, 79-6389
 Cell Transformation, Neoplastic
 79-6389

Chordoma
 IgG
 Antigen-Antibody Complex, 79-6505

Chromatids
 Benz(a)anthracene, 7-Bromomethyl-
 Chromosome Aberrations, 79-6319
 Benzo(a)pyrene
 Chromosome Aberrations, 79-6319
 Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
 7,8,9,10-tetrahydro-
 Chromosome Aberrations, 79-6319
 Benzo(a)pyrene 4,5-Oxide
 Chromosome Aberrations, 79-6319
 Chromic Acid, Dipotassium Salt
 Chromosome Aberrations, 79-6138
 Dose-Response Study, 79-6138
 Chromium Chloride
 Chromosome Aberrations, 79-6136
 Citrinin
 Cell Cycle Kinetics, 79-6256
 Mutagenic Metabolite, 79-6256
 Dichromic Acid, Dipotassium Salt
 Chromosome Aberrations, 79-6136
 79-6138
 Dose-Response Study, 79-6138
 β -Dienestrol
 Fibroblasts, 79-6341

Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Cell Division, 79-6224

Methanesulfonic Acid, Methyl Ester-
 Chromosome Aberrations, 79-6145
 Lymphocytes, 79-6145

Mitomycin C

Caffeine, 79-6226

Cell Division, 79-6224

Platinum, Diamminedichloro-, *cis*-
 Lymphocytes, 79-6143

Mitosis, 79-6143

Psoralen, 8-Methoxy-
 Lymphocytes, 79-6359

Quinacrine

Chromosome Aberrations, 79-6145

Lymphocytes, 79-6145

Quinacrine Mustard

Chromosome Aberrations, 79-6145

Lymphocytes, 79-6145

Quinoline, 4-Nitro-, 1-Oxide

Cell Division, 79-6224

Radiation, Ionizing

Chromosome Aberrations, 79-6361

DNA Replication, 79-6362

Mitosis, 79-6362

12-O-Tetradecanoylphorbol-13-acetate

Chromatids (cont'd)
 12-O-Tetradecanoylphorbol-13-acetate
 79-6361

Rubber

Solvents, 79-6238

4,4'-Stilbenediol, α,α' -Diethyl-

7,8-Benzoflavone, 79-6341

Chromosome Aberrations, 79-6341

β -Dienestrol, 79-6341

Fibroblasts, 79-6341

4,4'-Stilbenediol, α,α' -Diethyl-, α,β -

Oxide

Fibroblasts, 79-6341

12-O-Tetradecanoylphorbol-13-acetate

Mitomycin C, 79-6273

Uridine, 5-Bromo-2'-deoxy-, 79-6273

Tritium

Chromosome Aberrations, 79-6353

Lymphocytes, 79-6353

Uridine, 79-6353

Ultraviolet Rays

Cell Division, 79-6224

Lymphocytes, 79-6359

Psoralen, 8-Methoxy-, 79-6359

Uridine, 5-Bromo-2'-deoxy-

Cell Cycle Kinetics, 79-6226

Chromosome Aberrations, 79-6225

Lymphocytes, 79-6225

Chromatin

Acetohydroxamic Acid, *N*-Fluorenyl-2-yl-

Binding Sites, Liver, 79-6168

DNA Adduct, 79-6168

Beryllium

Liver, Rat, 79-6134

Cell Cycle Kinetics

Liver, Rat, 79-6590

Cell Division

Liver, Rat, 79-6590

Hepatectomy

Physicochemical Properties, 79-6590

Virus, SV40

Acetylation, 79-6600

Cleavage Sites, 79-6440

DNA, Circular, 79-6440

DNA Restriction Enzyme, 79-6440

79-6444

Virus Replication, 79-6444

Chromic Acid

Lung Neoplasms

Occupational Hazard, 79-6115

Chromic Acid, Dipotassium Salt

Chromatids

Chromosome Aberrations, 79-6138

Dose-Response Study, 79-6138

DNA Repair

Fibroblasts, 79-6137

Chromium

Air Pollution

Epidemiology, Review, 79-6054

79-6105

Chromosome Aberrations

Cytotoxicity, 79-6136

Hexavalent, Trivalent Compounds

79-6136

Chromium Chloride

Cells, Cultured

Cytotoxicity, 79-6136

Chromatids

Chromosome Aberrations, 79-6136

Chromium Glycine

DNA Repair

Fibroblasts, 79-6137

Chromosome Aberrations

Benz(a)anthracene, 7-Bromomethyl-

Chromatids, 79-6319

Benzene

Mutagenic Activity, Review, 79-6004

Solvents, 79-6238

Benzo(a)pyrene

Chromatids, 79-6319

Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-

7,8,9,10-tetrahydro-

Chromosome Aberrations (cont'd)

Chromatids, 79-6319

Benzo(a)pyrene 4,5-Oxide

Chromatids, 79-6319

Burkitt's Lymphoma

Chromosomes, Human, 6-12, 79-6487

Cadmium Chloride

Metaphase, 79-6135

Oocytes, Hamster, 79-6135

Carcinogen, Chemical

Bioassays, Review, 79-6048

Risk Evaluation, Review, 79-6035

Chromic Acid, Dipotassium Salt

Chromatids, 79-6138

Chromium

Cytotoxicity, 79-6136

Hexavalent, Trivalent Compounds

79-6136

Chromium Chloride

Chromatids, 79-6136

Citrinin

Hamster V79 Cells, 79-6256

Dichromic Acid, Dipotassium Salt

Chromatids, 79-6136, 79-6138

Dimethylamine, *N*-Nitroso-

Drosophila melanogaster, 79-6205

79-6209

Sex Chromosomes, 79-6205

Growth Substances

Horse Serum, 79-6129

Guanidine, 1-Methyl-3-nitro-1-nitroso-

Arginine, 79-6224

Leukemia, Myelocytic

Radiation, Ionizing, 79-6367

Methane, Sulfinylbis-

Drosophila melanogaster, 79-6205

79-6209

Sex Chromosomes, 79-6205

Methanesulfonic Acid, Ethyl Ester

Drosophila melanogaster, 79-6209

Methanesulfonic Acid, Methyl Ester

Chromatids, 79-6145

Drosophila melanogaster, 79-6205

79-6209

Sex Chromosomes, 79-6205

Mitomycin C

Arginine, 79-6224

Caffeine, 79-6226

Morpholine, *N*-Nitroso-

Embryo, Hamster, 79-6180

Mutagens

Bioassays, Review, 79-6048

Feces, 79-6140

Paraffin Oil

Solvents, 79-6238

Platinum, Diamminedichloro-, *cis*-

Dose-Response Study, 79-6143

Quinacrine

Chromatids, 79-6145

Quinacrine Mustard

Chromatids, 79-6145

Quinoline, 4-Nitro-, 1-Oxide

Arginine, 79-6224

Radiation, Ionizing

Chromatids, 79-6361

Mouse, 79-6367

Risk Evaluation, Review, 79-6035

79-6068

Rubber

Solvents, 79-6238

4,4'-Stilbenediol, α,α' -Diethyl-

Chromatids, 79-6341

Tritium

Chromatids, 79-6353

Ultraviolet Rays

Arginine, 79-6224

Urea, Methyl Nitroso-

Drosophila melanogaster, 79-6205

79-6209

Sex Chromosomes, 79-6205

Uridine, 5-Bromo-2'-deoxy-

Chromatids, 79-6225

Chromosome Abnormalities

Burkitt's Lymphoma

Diagnosis and Prognosis, 79-6524

- Chromosomes**
 Plasmacytoma
 Immunoglobulins, Light Chain
 79-6491
 Teratoid Tumor
 Cell Differentiation, Review, 79-6089
 Virus, SV40
 DNA, Viral, 79-6444
- Chromosomes, Human, 6-12**
 Burkitt's Lymphoma
 Chromosome Aberrations, 79-6487
 Virus, Baboon C-Type RNA Tumor
 Virus Replication, 79-6421
- Chromosomes, Human, 13-15**
 Burkitt's Lymphoma
 Chromosome Abnormalities, Review
 79-6127
 Virus, Baboon C-Type RNA Tumor
 Virus Replication, 79-6422
 Virus, Epstein-Barr
 Chromosome Aberrations, Review
 79-6078
- Chromosomes, Human, 19-20**
 Virus, Baboon C-Type RNA Tumor
 Virus Replication, 79-6422
- Chromosomes, Human, 21-22**
 Leukemia, Myeloblastic
 Immune Response, 79-6522
 Karyotyping, 79-6522
- Chrysene**
 Aryl Hydrocarbon Hydroxylases
 Enzyme Inhibition, 79-6313
 Diol Epoxides
 Carcinogenic Metabolite, Review
 79-6015
 Mutagenic Activity, 79-6304
- Chrysene, 1,2-Dihydro-**
 Skin Neoplasms
 Papilloma, 79-6304
- Chrysene, 1,2-Dihydroxy-3,4-oxy-1,2,3,4-**
 tetrachloro-
 Aroclor 1254
 Carcinogenic Metabolite, 79-6305
- Chrysene, 1,2-Dihydroxy-3,4-oxy-1,2,3,4-**
 tetrahydro-
 Ames Test
 Mutagenic Activity, 79-6304
- Chrysene, 1-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Chrysene, 3-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Chrysene, 6-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
 Skin Neoplasms
 Carcinoma, Epidermoid, 79-6305
- Chrysene, 7-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Chrysene, 9-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Chrysene, 11-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Chrysene, 12-Fluoro-5-methyl-**
 Ames Test
 Mutagenic Activity, 79-6305
- Citrinin**
 Chromatids
 Cell Cycle Kinetics, 79-6256
 Mutagenic Metabolite, 79-6256
 Chromosome Aberrations
 Hamster V79 Cells, 79-6256
- Citrinin (cont'd)**
 Microsomes, Liver
 Mutagenic Metabolite, 79-6256
- Clostridium welchii***
 Interferon
 Toxicity, 79-6463
- Coal**
 Gasification
 Epidemiology, Review, 79-6097
 Lung Neoplasms
 Occupational Hazard, 79-6585
 Occupational Hazard
 Epidemiology, Australia, 79-6585
- Coal Tar**
 Occupational Hazard
 Epidemiology, Review, 79-6097
 Smoking
 Co-carcinogenic Effect, Review
 79-6053
- Cobalt Chloride**
 Glutathione
 Gastrointestinal System, 79-6219
- Colitis, Ulcerative**
 Gastrointestinal Neoplasms
 Precancerous Conditions, Review
 79-6101
 Intestinal Neoplasms
 Precancerous Conditions, 79-6558
- Collagen**
 Plutonium
 Alpha Particles, 79-6372
- Colonic Neoplasms**
 Adenocarcinoma
 Hydrazine, 1,2-Dimethyl-, 79-6177
 Immunity, Cellular, Review, 79-6087
 Immunotherapy, Review, 79-6087
 Urea, Methyl Nitroso-, 79-6208
 Adenoma
 Urea, Methyl Nitroso-, 79-6208
 Antigens, Neoplasm
 Antigen-Antibody Reactions, Review
 79-6087
 5 β -Cholan-24-oic Acid, 3 α ,7 α -
 Dihydroxy-
 Bile Acids and Salts, 79-6208
 5 β -Cholan-24-oic Acid, 3 α ,12 α -
 Dihydroxy-
 Bile Acids and Salts, Review, 79-6051
 Diet
 Epidemiology, Review, 79-6051
 DNA
 Carrier Proteins, 79-6177
 Deoxyribonuclease, 79-6177
 Methane, Azoxy-
 Dietary Fiber, 79-6204
 Mutagens
 Feces, 79-6575
 Neoplasms, Multiple Primary
 Genetics, 79-6540
 Urea, Methyl Nitroso-
 5 β -Cholan-24-oic Acid, 3 α ,7 α -
 Dihydroxy-, 79-6208
 Dietary Fiber, 79-6204
- Complement**
 Hepatoma
 Antibody-Dependent Cell Cytotoxicity
 79-6507
 Growth, 79-6507
 Intestinal Neoplasms
 Immune Serums, 79-6513
 Sarcoma
 Cytotoxicity Assay, 79-6500
 Trypan Blue
 Cell Membrane, 79-6488
- Concanavalin A**
 Aryl Hydrocarbon Hydroxylases
 B-Lymphocytes, 79-6296
 Dietary Fats
 Lymphocyte Transformation, 79-6516
 Lymphocyte Transformation
 DNA Replication, 79-6465
- Concanavalin A (cont'd)**
 Virus, SV40
 Lymphocyte Transformation, 79-6448
- Contact Inhibition**
 Cell Transformation, Neoplastic
 Cells, Cultured, Review, 79-6091
 Fibroblasts, 79-6091
 Melanoma
 Cells, Cultured, Review, 79-6091
 Sarcoma
 Cells, Cultured, Review, 79-6091
- Contraceptives, Oral**
 Breast Neoplasms
 Epidemiology, Review, 79-6116
 Hepatoma
 Epidemiology, 79-6574
 Mammary Neoplasms, Experimental
 Histological Study, Dog, 79-6350
 Ovarian Neoplasms
 Risk Factors, 79-6573
 Uterine Neoplasms
 Adenocarcinoma, 79-6577
- Copper**
 Feces
 Catalase, 79-6140
 Hydrazine
 DNA Repair, 79-6141
 Occupational Hazard
 Epidemiology, Review, 79-6054
- Corn Oil**
 Aflatoxin B1
 Enzyme Activation, 79-6279
 Hepatoma
 Aflatoxin B1, 79-6279
- Corticosteroids**
 Gastritis
 Hemorrhage, 79-6550
- Cortisol**
 Virus, Herpes Simplex 1
 Virus Replication, 79-6427
 Virus, Herpes Simplex 2
 Virus Replication, 79-6427
- Cortisol Sodium Succinate**
 Virus, Epstein-Barr
 DNA Replication, 79-6432
- Corynebacterium parvum***
 Fibrosarcoma
 Growth, 79-6363
 Transplantation, Homologous, 79-6493
- Cosmetics**
 Ethanol, N-Nitrosoiminodi-
 Risk Factors, Review, 79-6062
- Coumarin**
 Bile Duct Neoplasms
 Metabolism, Review, 79-6066
 Skin Neoplasms
 Carcinogenic Potential, Review
 79-6066
- p-Cresol, 2,6-Di-tert-butyl-**
 Diet
 Co-carcinogenic Effect, Mouse
 79-6110
 Lung Neoplasms
 Carbamic Acid, Ethyl Ester, 79-6110
 Diethylamine, N-Nitroso-, 79-6110
- Cycasin**
 Ames Test
 Enzyme Activation, 79-6146
 Beta-Glucosidases
 Ames Test, 79-6146
- Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -**
 Isomer
 Diet
 Hepatocarcinogenesis, 79-6259
- 1,2-Cyclohexanedione**
 Ames Test
 Mutagenic Activity, 79-6160

4-Cyclohexene-1,2-dicarboximide, N-(Tri-chloromethyl)thio-
Ames Test
S9 Fraction, 79-6157

Cycloheximide

Amino Acids
Liver, Rat, 79-6598
Mutation
Ribosomes, 79-6159
Neurospora crassa
Drug Resistance, 79-6159
Ribosomes, 79-6159
12-*O*-Tetradecanoylphorbol-13-acetate
5,8,11,14-Eicosatetranic Acid
79-6277

Cyclopenta(a)phenanthren-17-one, 15,16-

Dihydro-11-methyl-
Carcinogenic Metabolite
Enzyme Activation, 79-6303
DNA Adducts
Isolation and Characterization
79-6303

Cyclopenta(cd)pyrene

Ames Test
Soot Extract, 79-6326

Cyclophosphamide

Bladder Diseases
Cystitis, 79-6580
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-6580
DNA
Antinuclear Factors, 79-6466
T-Lymphocytes, 79-6466
Fibrosarcoma
Transplantation Immunology, 79-6161
Leukemia, Myeloblastic
Drug Therapy, 79-6009
Lung Neoplasms
Neoplasm Metastasis, 79-6161
Mutation
Yeasts, 79-6191
Radiation, Ionizing
Neoplasm Metastasis, 79-6161
Sarcoma, Reticulum Cell
Immunosuppression, 79-6009

Cyprosterone Acetate

Mammary Neoplasms, Experimental
Carcinogenic Potential, Dog, 79-6352

Cystadenocarcinoma

Ovarian Neoplasms
Epidemiology, Dog, 79-6121

Cystadenoma

Ovarian Neoplasms
Epidemiology, Dog, 79-6121

Cysteine

Acetanilide, 4'-Hydroxy-
Hepatotoxic Metabolite, Review
79-6007
Carbon Tetrachloride
Metabolism, 79-6149
Disulfide, Bis(dimethylthiocarbonyl)-
Mutagenic Activity, 79-6199

Cystitis

Bladder Diseases
Cyclophosphamide, 79-6580

Cytochalasin B

Diethylamine, N-Nitroso-
Cell Transformation, Neoplastic
79-6195
Lymphoma
Plant Agglutinins, 79-6593
Vinblastine Sulfate
Cell Aggregation, 79-6593

Cytochrome P-450

Acetamide, N-Fluoren-2-yl-
Ames Test, 79-6166
Benzo(a)pyrene
Aryl Hydrocarbon Hydroxylases
79-6318

Cytochrome P-450 (cont'd)

Chloral Hydrate
Epoxide Metabolites, 79-6151

Cytosine, 5-Methyl-

Virus, Herpes Saimiri
DNA, Viral, 79-6425

Deoxyribonuclease

Colonic Neoplasms
DNA, 79-6177

D-2-Deoxyribose

see *D-erythro*-Pentose, 2-Deoxy-

Dermatitis, Contact

Ultraviolet Rays
DNA Repair, 79-6354

Dexamethasone

DNA-RNA Hybridization, 79-6395
Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor
79-6395
Virus, Murine Mammary Tumor
RNA, Viral, 79-6395

Dexamethasone Sodium Phosphate

Virus, Epstein-Barr
DNA Replication, 79-6432

Dextran, (Diethylamino)ethyl Ester

Poly U
DNA, Binding, 79-6265

Dextrans

Hepatoma
Endocytosis, 79-6229
Myeloma Proteins
Antigen-Antibody Reactions, 79-6490
Plasmacytoma
Binding Sites, Antibody, 79-6490

Diabetes Mellitus

Uterine Neoplasms
Drug Therapy, 79-6568

Diallate

see Carbamic Acid, Diisopropylthio-, S
-(2,3-Dichloroallyl) Ester

Dibenz(a,h)anthracene

Aryl Hydrocarbon Hydroxylases
B-Lymphocytes, 79-6296, 79-6313
5,6-Benzoflavone

Aryl Hydrocarbon Hydroxylases
79-6313

7,8-Benzoflavone

Aryl Hydrocarbon Hydroxylases
79-6313

Diol Epoxides

Carcinogenic Metabolite, Review
79-6015

Plant Agglutinins

Aryl Hydrocarbon Hydroxylases
79-6296

1-Propanone, 2-Methyl-1,2-di-3-pyridyl-,
Tartrate

Aryl Hydrocarbon Hydroxylases
79-6313

Valeric Acid, 2,2-Diphenyl-, 2-(Die-
thylamino)ethyl Ester

Aryl Hydrocarbon Hydroxylases
79-6313

Dibenzo(a,h)pyrene

Carcinogenic Activity
Polarographic Behavior, 79-6330

Dibenzo(a,i)pyrene

Ames Test
Mutagenic Activity, 79-6169

Dibenzo(b,def)chrysene

Sarcoma
Carcinogenic Activity, 79-6330

Dibenzo-p-dioxin

Aryl Hydrocarbon Hydroxylases
Chlorinated Analogs, 79-6249

Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-

Aryl Hydrocarbon Hydroxylases
Cells, Cultured, 79-6249
B-Lymphocytes, 79-6313
Benz(a)anthracene, 7,12-Dimethyl-
DNA, Binding, 79-6327
Benzo(a)pyrene
DNA, Binding, 79-6327
DNA, Binding
Liver, Rat, 79-6250
Environmental Hazard
Quantitation Method, Review, 79-6012
RNA, Ribosomal
Nucleotides, Binding, 79-6250
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6327

Dibenzofuran

Aryl Hydrocarbon Hydroxylases
Chlorinated Analogs, 79-6249

Dibutyl Cyclic AMP

Benz(a)anthracene, 7,12-Dimethyl-
DNA, Binding, 79-6294
Ornithine Decarboxylase
Precancerous Conditions, 79-6275

Dichromic Acid, Dipotassium Salt

Cells, Cultured
Cytotoxicity, 79-6136
Chromatids
Chromosome Aberrations, 79-6136
79-6138
Dose-Response Study, 79-6138

Dichromic Acid, Disodium Salt

Ames Test
S9 Fraction, 79-6157

Dieldrin

Carcinogenic Activity
Mouse, Rat, Review, 79-6010
Carcinogenic, Mutagenic Activity
Bioassays, Review, 79-6048
Diet
Hepatocarcinogenesis, 79-6259
Porphyria
Hepatocarcinogenesis, Review
79-6005

Dienestrol

Peroxidases
Metabolism, 79-6024

β -Dienestrol

Chromatids
Fibroblasts, 79-6341
4,4'-Stilbenediol, α,α' -Diethyl-
Chromatids, 79-6341

Diet

Breast Neoplasms
Epidemiology, 79-6571
Milk, Eggs, 79-6571
Carcinogen, Chemical
Metabolism, Review, 79-6040
5 β -Cholan-24-oic Acid, 3 α -Hydroxy-
Metabolism, 79-6162
5 β -Cholan-24-oic Acid, 3 α -Hydroxy-, 3 α -
Sulfate
Metabolism, 79-6162
Colonic Neoplasms
Epidemiology, Review, 79-6051
p-Cresol, 2,6-Di-*tert*-butyl-
Co-carcinogenic Effect, Mouse
79-6110
Digestive System Neoplasms
Epidemiology, Australia, 79-6586
Epidemiology, Review, 79-6099
Esophageal Neoplasms
Pyridoxol, 79-6565
Gastrointestinal Neoplasms
Epidemiology, Review, 79-6101
Neoplasms
Epidemiology, Review, 79-6022
79-6104

Dietary Fats

Benz(a)anthracene, 7,12-Dimethyl-

Dietary Fats (cont'd)

- Microsomes, Liver, 79-6301
- Concanavalin A
- Lymphocyte Transformation, 79-6516
- Hepatoma
- Aflatoxin B1, 79-6279
- Intestinal Neoplasms
- Epidemiology, Review, 79-6114
- Mammary Neoplasms, Experimental
- Benz(a)anthracene, 7,12-Dimethyl-79-6301, 79-6516
- Neoplasms
- Epidemiology, Review, 79-6026

Dietary Fiber

- Colonic Neoplasms
- Methane, Azoxy-, 79-6204
- Urea, Methyl Nitroso-, 79-6204
- Intestinal Neoplasms
- Epidemiology, Britain, 79-6559
- Hydrazine, 1,2-Dimethyl-, 79-6176
- Pentoses, 79-6559

Dietary Proteins

- Aflatoxin B1
- Alkaline Phosphatase, 79-6280
- Aminotransferases, 79-6280
- Lactate Dehydrogenase, 79-6280
- Aflatoxin M1
- Metabolism, Rat, 79-6280
- Aflatoxin P1
- Metabolism, Rat, 79-6280

Diethylamine, 2,2'-Dichloro-N-methyl-

- Mutation
- Yeasts, 79-6191

Diethylamine, N-Nitroso-

- Cell Transformation, Neoplastic
- Carcinogenic Metabolite, 79-6288
- Tissue Culture, 79-6195
- Chromosome Aberrations
- Drosophila melanogaster*, 79-6205
- 79-6209
- Cytochalasin B
- Cell Transformation, Neoplastic
- 79-6195
- DNA Polymerase
- DNA Repair, 79-6190
- DNA Replication, 79-6190
- Precancerous Conditions, 79-6190
- DNA Repair
- Hepatocarcinogenicity, 79-6184
- Liver, Rat, 79-6184
- Esophageal Neoplasms
- Food Contamination, 79-6197
- Hepatoma
- Dose-Response Study, 79-6193
- Hemeostasis, 79-6193
- Neoplasm Metastasis, 79-6195
- Lactate Dehydrogenase
- Cell Membrane Permeability, 79-6192
- Liver Neoplasms
- Choline, 79-6194
- Precancerous Conditions, 79-6194
- Lung Neoplasms
- p-Cresol, 2,6-Di-tert-butyl-, 79-6110
- Polychlorobiphenyl Compounds
- Metabolism, Review, 79-6112
- Proteins
- Amino Acid Incorporation, 79-6192
- Liver, Rat, 79-6192

Digestive System Neoplasms

- Alcoholic Beverages
- Epidemiology, Australia, 79-6586
- Bracken Fern
- Epidemiology, Review, 79-6022
- Diet
- Epidemiology, Australia, 79-6586
- Epidemiology, Review, 79-6099
- Dipropylamine, 2-Hydroxy-N-nitroso-2'-oxo-
- Histological Study, Hamster, 79-6196
- Environmental Hazard
- Epidemiology, Spain, Review, 79-6111
- Ethnic Groups
- Epidemiology, Review, 79-6099

Digestive System Neoplasms (cont'd)

- Mycotoxins
- Fusarium*, Review, 79-6098
- Polish Migrants
- England, Wales, 79-6557
- Digitalis
- Uterine Neoplasms
- Drug Therapy, 79-6568
- Dimethylamine, N-Nitroso-
- Acetamide, N-Fluoren-2-yl-
- DNA Repair, 79-6170
- Age Factors
- Metabolism, Mouse, 79-6183
- Air Pollution
- Occupational Hazard, 79-6182
- Chromosome Aberrations
- Drosophila melanogaster*, 79-6205
- 79-6209
- Sex Chromosomes, 79-6205
- DNA, Alkylation
- Carcinogenic Metabolite, Review
- 79-6064
- DNA Repair
- Chromatin, Review, 79-6063
- Liver, Rat, 79-6184
- Esophageal Neoplasms
- Food Contamination, 79-6197
- Esophagus
- DNA Adducts, 79-6315
- Guanine, 7-Methyl-
- DNA Adducts, 79-6315
- DNA, Alkylation, 79-6186
- DNA Repair, 79-6170
- Hemangioendothelioma
- Dose-Response Study, Rat, 79-6188
- Hepatoma
- Cell Cycle Kinetics, 79-6186
- DNA, Alkylation, 79-6186
- Dose-Response Study, Rat, 79-6188
- Lactate Dehydrogenase
- Cell Membrane Permeability, 79-6192
- Lactic Acid
- Lung, Mouse, 79-6187
- Leukemia, Lymphocytic
- Phorbol, 79-6189
- Liver Neoplasms
- Hyperplasia, 79-6188
- Phorbol, 79-6189
- Phorbol Esters, 79-6189
- Liver Regeneration
- Cell Cycle Kinetics, 79-6186
- Lung Neoplasms
- Lactic Acid, 79-6187
- Phosphotransferases, ATP, 79-6187
- Maternal-Fetal Exchange
- Tissue Distribution, 79-6183
- Nitrous Acid, Sodium Salt
- Stomach, Hamster, 79-6180
- Proteins
- Amino Acid Incorporation, 79-6192
- Liver, Rat, 79-6192
- Peptide Chain Initiation, 79-6185
- Purine, 2-Amino-6-methoxy-
- DNA Adducts, 79-6315
- DNA, Alkylation, 79-6186
- DNA Repair, 79-6170
- Pyelonephritis
- Dose-Response Study, Rat, 79-6188
- RNA, Messenger
- Liver, Mouse, 79-6185
- RNA, Transfer Methyltransferases
- Polyribosomes, 79-6185
- Urea, Hydroxy-
- Cell Cycle Kinetics, 79-6186

Diphenylamine

- Ascorbic Acid
- Nitrosation, 79-6245

Dipropylamine, 2-Hydroxy-N-nitroso-2'-oxo-

- Adenocarcinoma
- Neoplasm Metastasis, 79-6196
- Digestive System Neoplasms
- Histological Study, Hamster, 79-6196
- Pancreatic Neoplasms

Dipropylamine, 2-Hydroxy-N-nitroso-2'-oxo- (cont'd)

- Adenocarcinoma, 79-6196
- Neoplasms, Multiple Primary, 79-6196
- Respiratory Tract Neoplasms
- Histological Study, Hamster, 79-6196
- Urogenital Neoplasms
- Histological Study, Hamster, 79-6196

Disulfide, Bis(diethylthiocarbamoyl)-

- Methanol, (Methyl-ONN-azoxy)-, Acetate (Ester)
- DNA Replication, 79-6148

Disulfide, Bis(dimethylthiocarbamoyl)-

- Ames Test
- Mutagenic Activity, 79-6199
- S9 Fraction, 79-6199
- Cysteine
- Mutagenic Activity, 79-6199
- Glutathione
- Mutagenic Activity, 79-6199

DNA

- Colonic Neoplasms
- Carrier Proteins, 79-6177
- Deoxyribonuclease, 79-6177
- Cyclophosphamide
- Antinuclear Factors, 79-6466
- T-Lymphocytes, 79-6466
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
- Antinuclear Factors, 79-6466
- T-Lymphocytes, 79-6466
- Leukemia
- Radiation, Ionizing, 79-6591
- Methanesulfonic Acid, Methyl Ester
- Antinuclear Factors, 79-6466
- T-Lymphocytes, 79-6466
- Plasmacytoma
- Immunoglobulins, Light Chain
- 79-6491
- Radiation, Ionizing
- Hydroxylapatite Elution Assay
- 79-6591
- Rhodamine B
- Strand Breaks, 79-6264
- Rhodamine 6G
- Strand Breaks, 79-6264
- Urea, Methyl Nitroso-
- Antinuclear Factors, 79-6466
- T-Lymphocytes, 79-6466

DNA, Bacterial

- Agrobacterium tumefaciens*
- Transformation, Genetic, 79-6037
- Hydrazine, 1,2-Dimethyl-
- Transforming Activity, 79-6174
- Virus, SV40
- Transformation, Genetic, 79-6442

DNA, Circular

- Virus, SV40
- Chromatin, 79-6440

DNA, Mitochondrial

- Saccharomyces cerevisiae*
- Mutation, 79-6152

DNA, Neoplasm

- Sarcoma, Mast Cell
- DNA-RNA Hybridization, 79-6594

DNA Polymerase

- Diethylamine, N-Nitroso-
- DNA Repair, 79-6190
- DNA Replication, 79-6190
- Precancerous Conditions, 79-6190
- Virus, Hepatitis
- Antigens, Viral, Review, 79-6080

DNA Repair

- Acetamide, N-Fluoren-2-yl-
- Guanine, 7-Methyl-, 79-6170
- Purine, 2-Amino-6-methoxy-, 79-6170
- Acridine
- Carcinogenic Potential, Review
- 79-6013
- Alkylating Agents
- Mutation, Review, 79-6067
- Xeroderma Pigmentosum, 79-6067

DNA Repair (cont'd)

- Anemia, Aplastic
 - Chromosome Aberrations, Review 79-6092
- Ataxia Telangiectasia
 - Chromosome Aberrations, Review 79-6092
- Carcinogen, Chemical
 - Chromatin, Review, 79-6063
 - Toxicity, Review, 79-6034
- Chromic Acid, Dipotassium Salt
 - Fibroblasts, 79-6137
- Chromium Glycine
 - Fibroblasts, 79-6137
- Dermatitis, Contact
 - Ultraviolet Rays, 79-6354
- Diethylamine, *N*-Nitroso-
 - DNA Polymerase, 79-6190
 - Hepatocarcinogenicity, 79-6184
 - Liver, Rat, 79-6184
- Dimethylamine, *N*-Nitroso-
 - Acetamide, *N*-Fluorenyl-2-yl-, 79-6170
 - Chromatin, Review, 79-6063
 - Guanine, 7-Methyl-, 79-6170
 - Liver, Rat, 79-6184
 - Purine, 2-Amino-6-methoxy-, 79-6170
- Dwarfism
 - Chromosome Aberrations, Review 79-6092
 - Fibroblasts, 79-6377
 - Ultraviolet Rays, 79-6377
 - Virus, Herpes Simplex 1, 79-6377
- Formaldehyde
 - Yeasts, 79-6163
- Hydrazine
 - Copper, 79-6141
 - Iron, 79-6141
 - Manganese, 79-6141
 - Isonicotinic Acid, 2-(2-(Benzylcarbamoyl)ethyl)hydrazide
 - Manganese, 79-6141
 - Isonicotinic Acid Hydrazide
 - Fibroblasts, 79-6141
 - Manganese, 79-6141
 - Isonicotinic Acid, 2-Isopropylhydrazide
 - Manganese, 79-6141
 - Lupus Erythematosus, Systemic
 - Caffeine, 79-6358
- Mutation
 - Yeasts, 79-6191
- Porphyria
 - Ultraviolet Rays, 79-6354
- Quinoline, 4-Nitro-, 1-Oxide
 - Caffeine, 79-6358
 - Lymphocytes, 79-6358
 - Virus, LPV, 79-6227
 - Virus, RNA Tumor, 79-6227
- Radiation, Ionizing
 - Cell Transformation, Neoplastic 79-6361
 - Mutation, Review, 79-6067
 - Xeroderma Pigmentosum, 79-6067
- Ultraviolet Rays
 - Caffeine, 79-6358
 - Lymphocytes, 79-6358
 - Mutation, Review, 79-6067
 - Xeroderma Pigmentosum, 79-6067
- Urea, Methyl Nitroso-
 - HeLa Cells, 79-6466
- Virus, SV40
 - Ultraviolet Rays, 79-6356
- Xeroderma Pigmentosum
 - Caffeine, 79-6357
 - Chromosome Aberrations, Review 79-6092
 - Complementation Group, 79-6355
 - Ultraviolet Rays, 79-6354, 79-6355
 - 79-6356, 79-6357
 - Virus, SV40, 79-6355

DNA Replication

- Diethylamine, *N*-Nitroso-
 - DNA Polymerase, 79-6190
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Gastric Mucosa, 79-6222
- Leukemia, Lymphocytic

DNA Replication (cont'd)

- Lipopolysaccharides, 79-6471
 - Lymphocyte Transformation
 - Concanavalin A, 79-6465
 - Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
 - Colon, Rat, 79-6148
 - Disulfide, Bis(diethylthiocarbamoyl)- 79-6148
 - Porphyria
 - Ultraviolet Rays, 79-6354
 - Radiation, Ionizing
 - Chromatids, 79-6362
 - Stomach Neoplasms
 - Neoplasm Invasiveness, 79-6221
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - Lymphocyte Culture Test, Mixed 79-6270
 - Virus, Avian Sarcoma
 - RNA, Viral, 79-6379
 - Virus, Epstein-Barr
 - Cortisol Sodium Succinate, 79-6432
 - Dexamethasone Sodium Phosphate 79-6432
 - Virus, SV40
 - Antigens, Neoplasm, 79-6443
 - Phenylalanine, 4-Fluoro-, 79-6446
- DNA Restriction Enzyme**
- Virus, Moloney Murine Sarcoma
 - Cleavage Sites, 79-6413
 - Virus, Polyoma
 - Antigens, Neoplasm, 79-6439
 - Virus, SV40
 - Chromatin, 79-6440, 79-6444
- DNA, Viral**
- Fibrosarcoma
 - Virus, Adeno 2 - SV40 Hybrid 79-6458
 - Lymphoma
 - Virus, Herpes Saimiri, 79-6425
 - Sarcoma
 - Virus, Adeno 2 - SV40 Hybrid 79-6458
 - Virus, Adeno 2
 - Cleavage Sites, 79-6391
 - Endonucleases, 79-6391
 - Virus, Adeno Mouse FL
 - Cleavage Sites, 79-6391
 - Endonucleases, 79-6391
 - Virus, Adeno 2 - SV40 Hybrid
 - Ultraviolet Rays, 79-6458
 - Virus, Bovine Papilloma
 - DNA-RNA Hybridization, 79-6420
 - Virus, Epstein-Barr
 - Lymphocyte Transformation, 79-6430
 - Nucleic Acid Renaturation, 79-6430
 - Virus, Hamster Papova
 - Endonucleases, 79-6417
 - Isolation and Characterization 79-6417
 - Virus, Harvey Murine Sarcoma
 - Transformation, Genetic, 79-6410
 - Virus, Herpes Saimiri
 - Cytosine, 5-Methyl-, 79-6425
 - Endonucleases, 79-6425
 - Virus, Moloney Murine Sarcoma
 - Reverse Transcriptase, 79-6413
 - Virus, Murine Mammary Tumor
 - A-Type Particles, 79-6394
 - Virus, Polyoma
 - Cell Transformation, Neoplastic 79-6439
 - Deletion Mutants, 79-6433
 - Escherichia coli*, 79-6434
 - Reentry Kinetics, 79-6436
 - Transformation, Genetic, 79-6434
 - Virus-Like Particles, 79-6437
 - Virus Replication, 79-6436
 - Virus, SV40
 - Chromosomes, 79-6444
 - Micronucleation Technique, 79-6443
- Dopamine Beta-Hydroxylase**
- Pheochromocytoma
 - Pyrocatechol, 4-(2-Aminoethyl)- 79-6547

Drosophila melanogaster

- Benzene, (Epoxymethyl)-
 - Mutagenic Activity, 79-6248
 - 1,3-Butadiene, 1-Chloro-
 - Mutagenic Activity, 79-6158
 - 1,3-Butadiene, 2-Chloro-
 - Mutagenic Activity, 79-6158
 - Butane, 1,4-Dichloro-2,3-epoxy-
 - Mutagenic Activity, 79-6158
 - 2-Butene, 1,4-Dichloro-
 - Mutagenic Activity, 79-6158
 - Carbamic Acid, Ethyl Ester
 - Mutagenic Activity, 79-6198
 - Sex Chromosomes, 79-6198
 - Dimethylamine, *N*-Nitroso-
 - Chromosome Aberrations, 79-6205
 - 79-6209
 - Food Contamination
 - Sex Chromosomes, 79-6364
 - Methane, Sulfinylbis-
 - Chromosome Aberrations, 79-6205
 - 79-6209
 - Methanesulfonic Acid, Ethyl Ester
 - Chromosome Aberrations, 79-6209
 - Methanesulfonic Acid, Methyl Ester
 - Chromosome Aberrations, 79-6205
 - 79-6209
 - Mitomycin C
 - Mutation, 79-6365
 - Mutation
 - Sex Chromosomes, 79-6365
 - Radiation, Ionizing
 - Mutagenic Activity, 79-6198
 - Mutation, 79-6365
 - Sex Chromosomes, 79-6198
 - Styrene
 - Mutagenic Activity, 79-6248
 - Urea, Methyl Nitroso-
 - Chromosome Aberrations, 79-6205
 - 79-6209
 - Uridine, 2'-Deoxy-5-fluoro-
 - Mutation, 79-6365
- Drug Therapy**
- Erythroleukemia
 - Neoplasms, Multiple Primary, 79-6009
 - Leukemia, Myeloblastic
 - Antineoplastic Agents, 79-6009
 - Lymphoma
 - Neoplasms, Multiple Primary, 79-6009
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester
 - Epidemiology, 79-6155
- Dwarfism**
- DNA Repair
 - Chromosome Aberrations, Review 79-6092
 - Fibroblasts, 79-6377
 - Ultraviolet Rays
 - DNA Repair, 79-6377
 - Virus, Herpes Simplex 1
 - DNA Repair, 79-6377
- Dyes**
- Food Additives
 - Mutagenic Activity, 79-6286
- Ear Neoplasms**
- Adenocarcinoma
 - Pectin, 79-6176
 - Astrocytoma
 - Radiotherapy, 79-6376
 - Benz(a)anthracene, 7,12-Dimethyl-4-Stilbenamine, *N,N*-Dimethyl- 79-6302
 - Oxidoreductases
 - Zymbal Gland, Rat, 79-6302
- 5,8,11,14-Eicosatetraenoic Acid**
- Erythroleukemia
 - 12-*O*-Tetradecanoylphorbol-13-acetate 79-6278
 - Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-
 - Platelet Aggregation, 79-6272
 - 12-*O*-Tetradecanoylphorbol-13-acetate

5,8,11,14-Eicosatetraenoic Acid (cont'd)
 Cycloheximide, 79-6277
 Fibroblasts, Chick Embryo, 79-6277
 Puromycin, 79-6277
 Thromboxanes
 Platelet Aggregation, 79-6272

Electrons
 Food Contamination
 Sex Chromosomes, 79-6364

Encephalitis
 Brain Neoplasms
 Virus, Herpes Simplex 2, 79-6532

Endometrial Hyperplasia
 Estrogens
 Menopause, 79-6348
 Estrone
 Receptors, Hormone, Review, 79-6028

Endonucleases
 Plasmacytoma
 Nucleic Acids, 79-6491
 Virus, Adeno 2
 DNA, Viral, 79-6391
 Virus, Adeno Mouse FL
 DNA, Viral, 79-6391
 Virus, Hamster Papova
 DNA, Viral, 79-6417
 Virus, Herpes Saimiri
 DNA, Viral, 79-6425

Endotoxins
 Amyloid
 Isolation and Characterization, Mouse
 79-6492

Environmental Hazard
 1,2-Benzisothiazolin-3-one, 1,1-Dioxide
 Risk Factors, 79-6578
 Carcinogen, Chemical
 Thresholds, Review, 79-6045, 79-6108
 Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-
 Quantitation Method, Review, 79-6012
 Digestive System Neoplasms
 Epidemiology, Spain, Review, 79-6111
 Ether, Bis(chloromethyl)-
 Quantitation Method, Review, 79-6012
 Ethyl Alcohol
 Risk Factors, 79-6578
 Fluorescent Dyes
 Carcinogenic Potential, Review
 79-6018
 Gastrointestinal Neoplasms
 Asbestos, 79-6569
 Glycine, N,N-Bis(carboxymethyl)-
 Risk Evaluation, Canada, Review
 79-6107
 Lung Neoplasms
 Asbestos, 79-6569
 Nitroso Compounds
 Precursors, Review, 79-6057
 Ovarian Neoplasms
 Epidemiology, Review, 79-6123
 Phenol, 2,4,5-Trichloro-
 Quantitation Method, Review, 79-6012
 Phosphorothioic Acid, O,O-Dimethyl-O-
 (2,4,5-trichlorophenyl)-
 Quantitation Method, Review, 79-6012
 Respiratory Tract Neoplasms
 Epidemiology, Spain, Review, 79-6111
 Smoking
 Risk Factors, 79-6578
 Toxicity
 Risk Evaluation, Canada, Review
 79-6107
 Urogenital Neoplasms
 Epidemiology, Spain, Review, 79-6111

Ependymoma
 Brain Neoplasms
 Urea, Nitroso-, 79-6201

Ephedrine
 Nitroso Compounds
 Precursors, Review, 79-6057

Epoxide Hydratases
 Benz(a)anthracene

Epoxide Hydratases (cont'd)
 Hepatocytes, Hamster, 79-6288
 Benzo(a)pyrene
 Mutagenic Metabolite, 79-6329
 Benzo(a)pyrene 4,5-Oxide
trans-Stilbene Oxide, 79-6316
 Cholanthrene, 3-Methyl-
 Hepatocytes, Hamster, 79-6288
trans-Stilbene Oxide
 Liver, Rat, 79-6316

Erythroleukemia
 Neoplasms, Multiple Primary
 Drug Therapy, 79-6009
 12-O-Tetradecanoylphorbol-13-acetate
 5,8,11,14-Eicosatetraenoic Acid
 79-6278
 Prostaglandins E, 79-6278
 Prostaglandins F, 79-6278
 Virus, Friend Murine Leukemia
 Immunosuppression, 79-6408
 12-O-Tetradecanoylphorbol-13-acetate
 79-6278

Escherichia coli
 2-Furanol, Tetrahydro-
 Mutagenic Metabolite, 79-6212
 Methanesulfonic Acid, Ethyl Ester
 Mutagenic Activity, 79-6206
 Pyrrolidine, 1-Nitroso-
 Mutagenic Activity, 79-6212
 Urea, 1-Butyl-1-nitroso-
 Mutagenic Activity, 79-6206
 Urea, Ethyl Nitroso-
 Mutagenic Activity, 79-6206
 Urea, Methyl Nitroso-
 Mutagenic Activity, 79-6206
 Urea, N-Nitroso-N-propyl-
 Mutagenic Activity, 79-6206
 Virus, Polyoma
 DNA, Viral, 79-6434
 Virus, SV40
 DNA-DNA Hybridization, 79-6442

Esophageal Neoplasms
 Alcoholic Beverages
 Epidemiology, 79-6564, 79-6565
 Epidemiology, Britain, 79-6560
 Benzylamine, N-Methyl-N-nitroso-
 Animal Model, Rat, 79-6233
 Mycotoxins, 79-6197
 2-Butanone, 3-((3-
 Methylbutyl)nitrosamino)-
 Food Contamination, 79-6197
 Mycotoxins, 79-6197
 Carcinoma
 Alcoholic Beverages, 79-6566
 Smoking, 79-6566
 Carcinoma, Epidermoid
 Benzylamine, N-Methyl-N-nitroso-
 79-6233
 Epidemiology, Israel, 79-6566
 Immunity, Cellular, 79-6511
 Pentylamine, N-Methyl-N-nitroso-
 79-6214
 Carcinoma, Papillary
 Benzylamine, N-Methyl-N-nitroso-
 79-6233
 Diethylamine, N-Nitroso-
 Food Contamination, 79-6197
 Dimethylamine, N-Nitroso-
 Food Contamination, 79-6197
 Esophagitis
 Genetics, 79-6563
 Ethnic Groups
 Epidemiology, Israel, 79-6566
 T-Lymphocytes
 Plant Agglutinins, 79-6511
 Opium
 Epidemiology, 79-6565
 Papilloma
 Benzylamine, N-Methyl-N-nitroso-
 79-6233
 Pentylamine, N-Methyl-N-nitroso-
 Dose-Response Study, Rat, 79-6214
 Precancerous Conditions
 Epidemiology, Iran, 79-6563
 Pyridoxol

Esophageal Neoplasms (cont'd)
 Diet, 79-6565
 Smoking
 Epidemiology, 79-6565
 Epidemiology, Review, 79-6126

Esophagus
 Benzo(a)pyrene
 DNA Adducts, 79-6315
 Benzo(a)pyrene, 7,8-Dihydro-7,8-
 dihydroxy-
 Carcinogenic Metabolite, 79-6315
 Benzo(a)pyrene, 7,8,9,10-Tetrahydro-
 7,8,9,10-tetrahydroxy-
 DNA Adducts, 79-6315
 Dimethylamine, N-Nitroso-
 DNA Adducts, 79-6315
 Pyrrolidine, 1-Nitroso-
 DNA Adducts, 79-6315

Estradiol
 Breast Neoplasms
 Genes, Embryonic, Review, 79-6030
 RNA, Ribosomal
 Genes, Embryonic, Review, 79-6030

Estradiol, 17-Ethynyl-
 Mammary Neoplasms, Experimental
 Hyperplasia, 79-6350

Estrogens
 Breast Neoplasms
 Dietary Fats, Review, 79-6029
 Receptors, Hormone, Review, 79-6346
 79-6347, 79-6349
 Endometrial Hyperplasia
 Menopause, 79-6348
 Mammary Neoplasms, Experimental
 Receptors, Hormone, Review, 79-6346
 Mitosis
 Cell Transformation, Neoplastic, Re-
 view, 79-6031
 Neoplasms
 Chromatin, Review, 79-6030
 Receptors, Hormone, Review, 79-6030
 Ovarian Neoplasms
 Epidemiology, Review, 79-6120
 Receptors, Hormone
 Cell Transformation, Neoplastic, Re-
 view, 79-6031
 Uterine Neoplasms
 Adenocarcinoma, 79-6567, 79-6577
 Dietary Fats, Review, 79-6029
 Epidemiology, Finland, 79-6568
 Epidemiology, Review, 79-6124
 Menopause, 79-6348

Estrone
 Endometrial Hyperplasia
 Receptors, Hormone, Review, 79-6028
 Uterine Neoplasms
 Adenocarcinoma, 79-6028

Ethane, 1,2-Dibromo-
 Ames Test
 Mutagenic Activity, Review, 79-6046
 Glutathione
 Carcinogenic Activity, 79-6150
 Imidazole-2-thiol, 1-Methyl-
 Carcinogenic Activity, 79-6150
 Microsomes
 Macromolecules, Binding, 79-6150
 Valeric Acid, 2,2-Diphenyl-, 2-(Di-
 thylamino)ethyl Ester, HCl
 Macromolecules, Binding, 79-6150

Ethane, 1,2-Dichloro-
 Ames Test
 Mutagenic Activity, Review, 79-6046
 Microsomes
 Macromolecules, Binding, 79-6150

**Ethane, 1,1,1-Trichloro-2,2-bis(p-
 chlorophenyl)-**
 Carcinogenic, Mutagenic Activity
 Bioassays, Review, 79-6048
 Liver Neoplasms
 Carcinogenic Potential, Review
 79-6047

Ethane, 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)- (cont'd)

- Occupational Hazard
- Epidemiology, Review, 79-6047
- Patulin
- Ribonuclease, 79-6257
- Porphyria
- Hepatocarcinogenesis, Review 79-6005
- RNA Polymerase
- RNA Replication, 79-6257

Ethanol, 2-Mercapto-
Leukemia, Lymphocytic
B-Lymphocytes, 79-6471

Ethanol, N-Nitrosoiminodi-
Cosmetics
Risk Factors, Review, 79-6062

Ether, Bis(chloromethyl)-
Environmental Hazard
Quantitation Method, Review, 79-6012
Occupational Hazard
Epidemiology, Review, 79-6113

Ethidium Bromide
Saccharomyces cerevisiae
Mutation, 79-6152

Ethyl Alcohol
Environmental Hazard
Risk Factors, 79-6578

Ethylene, Chloro-
Ames Test
Mutagenic Metabolite, 79-6165
Aryl Hydrocarbon Hydroxylases
Metabolism, Liver, 79-6165
Carcinogen, Environmental
Experimental Toxicology, Review 79-6104
Microsomes, Liver
Ames Test, 79-6151
Occupational Hazard
Epidemiology, Review, 79-6113

Ethylene, Chloro- Polymer
Air Pollution
Epidemiology, Review, 79-6105
Occupational Hazard
Toxicity, Review, 79-6102

Ethylene, 1,1-Dichloro-
Microsomes, Liver
Ames Test, 79-6151

Ethylene, 1,2-Dichloro-
Microsomes, Liver
Ames Test, 79-6151

Ethylene, 1,1-Dichloro-2,2-bis(p-chlorophenyl)-
Carcinogenic, Mutagenic Activity
Bioassays, Review, 79-6048

Ethylene Oxide
Hemoglobins
Alkylation, Review, 79-6049
Mutation
Risk Evaluation, Review, 79-6049

Ethylene, Tetrachloro-
Microsomes, Liver
Ames Test, 79-6151

Ethylene, Trichloro-
Acetyl Chloride, Dichloro-
Epoxide Metabolites, 79-6151
Hyperplasia
Pulmonary Alveoli, 79-6207
Nucleic Acid Replication
Lung, Rat, 79-6207
Pulmonary Surfactant
Lung, Rat, 79-6207
Structure-Activity Relationship
Epoxide Metabolites, 79-6151

Extrachromosomal Inheritance
Virus, Polyoma
Carcinogenic Potential, 79-6434

Eye Neoplasms

- Burkitt's Lymphoma
- Histopathological Study, 79-6554
- Carcinoma, Basal Cell
- Epidemiology, Sudan, 79-6554
- Carcinoma, Epidermoid
- Epidemiology, Sudan, 79-6554
- Melanoma
- Histopathological Study, 79-6554
- Retinoblastoma
- Epidemiology, Sudan, 79-6554

Feces

- Catalase
- Mutagenic Activity, 79-6140
- Colonic Neoplasms
- Mutagens, 79-6575
- Copper
- Catalase, 79-6140
- Manganese
- Mutagenic Activity, 79-6140
- Mutagens
- Ames Test, 79-6575

Fetal Globulins

- Carcinogen, Chemical
- Immune Response, Review, 79-6039
- Fibrosarcoma
- Growth, 79-6497
- Macrophages
- Transplantation Immunology, 79-6497
- Oncogenic Viruses
- Immune Response, Review, 79-6039
- Virus, Rous Sarcoma
- Cell Transformation, Neoplastic 79-6388

Fibroblasts

- Calcium
- Cell Division, 79-6385
- Cell Transformation, Neoplastic
- Contact Inhibition, 79-6091
- Homeostasis, 79-6385
- Chromic Acid, Dipotassium Salt
- DNA Repair, 79-6137
- Chromium Glycine
- DNA Repair, 79-6137
- β -Dienestrol
- Chromatids, 79-6341
- Dwarfism
- DNA Repair, 79-6377
- Isonicotinic Acid Hydrazide
- DNA Repair, 79-6141
- Magnesium
- Cell Division, 79-6385
- Phorbol Esters
- Glycoproteins, 79-6267
- Poly U
- DNA, Binding, 79-6265
- 4,4'-Stilbenediol, α,α' -Diethyl-
Chromatids, 79-6341
- 4,4'-Stilbenediol, α,α' -Diethyl-, α,β -
Oxide
- Chromatids, 79-6341
- 12-O-Tetradecanoylphorbol-13-acetate
- Cell Differentiation, 79-6271
- Virus, Rous Sarcoma
- Cell Transformation, Neoplastic 79-6385
- Glycoproteins, 79-6390

Fibroma

- Morpholine, N-Nitroso-
Carcinogenic Activity, Rat, 79-6215
- Soft Tissue Neoplasms
- Anthraquinone, 2-Methyl-1-nitro-
79-6262
- Virus, Vesicular Stomatitis
- Virus Replication, 79-6418

Fibronectins

- see Glycoproteins

Fibrosarcoma

- Benz(a)anthracene, 7,12-Dimethyl-
Radiation, Ionizing, 79-6363
- Transplantation, Homologous, 79-6297
- Transplantation Immunology, 79-6497
- Benzo(a)pyrene

Fibrosarcoma (cont'd)

- Genetics, Mouse, 79-6318
- Microsomes, Liver, 79-6318
- Cholanthrene, 3-Methyl-
Macrophages, 79-6495
- Membrane Proteins, 79-6596
- Neoplasm Transplantation, 79-6496
- Phosphoglycerate Kinase, 79-6306
- Sex Chromosomes, 79-6306
- Corynebacterium parvum*
Growth, 79-6363
- Cyclophosphamide
- Transplantation Immunology, 79-6161
- Fetal Globulins
- Growth, 79-6497
- Glycoproteins
- Tumorigenic Clone Cells, 79-6596
- Histocompatibility Antigens
- Antigen-Antibody Reactions, 79-6494
- Lymphocyte Cooperation, 79-6494
- T-Lymphocytes, 79-6494
- Hypersensitivity, Delayed
- Neoplasm Transplantation, 79-6495
- Hypothyroidism
- Neoplasm Metastasis, 79-6595
- Isoantibodies
- Growth, 79-6496
- IgG, 79-6496
- Immunoglobulins, Fc, 79-6496
- Lung
- Neoplasm Metastasis, 79-6493
- T-Lymphocytes
- Lymphocyte Depletion, 79-6493
- Macrophages
- Growth, 79-6497
- Radiation, Ionizing
- Growth, 79-6363
- Transplantation Immunology, 79-6363
- Skin Neoplasms
- Propionic Acid, 2-(p-Chlorophenoxy)-
2-methyl-, Ethyl Ester, 79-6154
- Thyroxine
- Neoplasm Metastasis, 79-6595
- Transplantation Immunology, 79-6595
- Transplantation, Homologous
- Corynebacterium parvum*, 79-6493
- Neoplasm Metastasis, 79-6493
- Radiation, Ionizing, 79-6493
- Ultraviolet Rays
- Immunity, Cellular, 79-6494
- Virus, Adeno 2 - SV40 Hybrid
DNA, Viral, 79-6458

Fluoranthene

- Ames Test
- Soot Extract, 79-6326

Fluoren-2-amine

- Ames Test
- Microsomes, Intestinal Mucosa 79-6178
- Mutagenic Activity, 79-6169
- Mutagenic Metabolite, 79-6167
- S9 Fraction, 79-6157
- S9 Fraction, Liver, Kidney, 79-6235

Bacteroides fragilis

- Mutagenic Metabolite, 79-6178
- Cholanthrene, 3-Methyl-
Aryl Hydrocarbon Hydroxylases 79-6235
- Mutagenic Activity, 79-6235
- Microsomes, Liver
- Mutagenic Metabolite, 79-6167

Fluorene, 2-Azido-

- Ultraviolet Rays
- Cytotoxicity, 79-6139

Fluorene, 2,5-Diazido-

- Ultraviolet Rays
- Cell Transformation, Neoplastic 79-6139

Fluorene, 2,7-Diazido-

- Ultraviolet Rays
- Cell Transformation, Neoplastic 79-6139

Fluorene, 2-Nitro-
Cell Transformation, Neoplastic
Carcinogenic Metabolite, 79-6288

Fluorescein, Disodium Salt
Air Pollution
Occupational Hazard, 79-6263

Fluorescent Dyes
Ames Test
Mutagenic Activity, Review, 79-6018
Environmental Hazard
Carcinogenic Potential, Review
79-6018
Saccharomyces cerevisiae
Mutagenic Activity, Review, 79-6018

Folic Acid
Nitroso Compounds
Precursors, Review, 79-6057

Food Additives
1,2-Benzisothiazolin-3-one, 1,1-Dioxide
Carcinogenic Potential, Review
79-6060
Classification
Risk Evaluation, Review, 79-6042
Dyes
Mutagenic Activity, 79-6286
Nitrous Acid
Carcinogenic Potential, Review
79-6060
Saccharomyces cerevisiae
Mutagenic Activity, 79-6286
Thresholds
Risk Evaluation, Review, 79-6106

Food Contamination
Aflatoxin B1
Fruit, 79-6281
Aflatoxin G1
Fruit, 79-6281
Benzoic Acid, 2,3,6-Trichloro-
Carcinogenic Potential, Review
79-6098
Drosophila melanogaster
Sex Chromosomes, 79-6364
Electrons
Sex Chromosomes, 79-6364
Esophageal Neoplasms
2-Butanone, 3-((3-
Methylbutyl)nitrosamino)-, 79-6197
Diethylamine, *N*-Nitroso-, 79-6197
Dimethylamine, *N*-Nitroso-, 79-6197
Mercury
Risk Evaluation, Canada, Review
79-6107
Nitric Acid
Risk Factors, Review, 79-6110
Nitrous Acid
Risk Factors, Review, 79-6110
Radiation, Ionizing
Sex Chromosomes, 79-6364
Zearalenone
Carcinogenic Potential, Review
79-6098

Formaldehyde
Nitrosamines
Hypermethylation, Review, 79-6059
Polycyclic Hydrocarbons
Hypermethylation, Review, 79-6059
Yeasts
DNA Repair, 79-6163
Mutagenic Activity, 79-6163

Fosfestrol
Spermatozoa
Mutagenic Activity, 79-6239

FSH
Testicular Neoplasms
Leydig Cell Tumor, 79-6351
Uterine Neoplasms
Adenocarcinoma, 79-6552

2-Furanol, Tetrahydro-
Escherichia coli
Mutagenic Metabolite, 79-6212

Gallbladder Diseases
Ovarian Neoplasms
Epidemiology, 79-6573

Gasoline
Nucleic Acid Replication
Lung, Rat, 79-6207

Gastrectomy
Stomach Neoplasms
Carcinoma, 79-6512
Epidemiology, 79-6561
Precancerous Conditions, Review
79-6094

Gastric Mucosa
Gastritis
Carcinoembryonic Antigen, 79-6512
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Carcinogenic Activity, 79-6218
Cell Membrane Permeability, 79-6218
DNA Replication, 79-6222
Ultrastructural Study, 79-6218

Gastrin
Stomach Neoplasms
Carcinoid Tumor, 79-6539

Gastritis
Breast Neoplasms
Hemorrhage, 79-6550
Carcinoembryonic Antigen
Gastric Mucosa, 79-6512
Hemorrhage
Antineoplastic Agents, 79-6550
Corticosteroids, 79-6550
Salicylic Acid, 79-6550
Polychlorobiphenyl Compounds
Carcinogenic Potential, Review
79-6112

Gastrointestinal Neoplasms
Adenoma
Precancerous Conditions, Review
79-6101
Adenomatosis, Familial Endocrine
Epidemiology, Review, 79-6100
Asbestos
Environmental Hazard, 79-6569
Epidemiology, Review, 79-6052
Colitis, Ulcerative
Precancerous Conditions, Review
79-6101
Diet
Epidemiology, Review, 79-6101
Enteritis, Regional
Genetics, Review, 79-6100
Hereditary Diseases
Epidemiology, Review, 79-6100
Nitric Acid
Epidemiology, Review, 79-6101
Polyps
Genetics, Review, 79-6100
Steroids
Epidemiology, Review, 79-6101

Gastrointestinal System
Cobalt Chloride
Glutathione, 79-6219
Maleic Acid, Diethyl Ester
Glutathione, 79-6219

Genetics
Breast Neoplasms
Epidemiology, Review, 79-6117
Colonic Neoplasms
Neoplasms, Multiple Primary, 79-6540
Esophageal Neoplasms
Esophagitis, 79-6563
Lymphoma
Virus, Murine Leukemia, 79-6405
Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor
79-6398
Nephroblastoma
Hamartoma, 79-6546
Stomach Neoplasms
Epidemiology, 79-6561
Uterine Neoplasms

Genetics (cont'd)
Neoplasms, Multiple Primary, 79-6540
Virus, AKR Murine Leukemia
Anti-Antibodies, 79-6404
Virus Replication, 79-6405

Giant Cell Tumors
Osteitis Deformans
Case Report, 79-6533

Glioblastoma Multiforme
Virus, RNA Tumor
Reverse Transcriptase, 79-6459
Virus-Like Particles, 79-6459

Glioma
Acid Phosphatase
Enzymatic Activity, 79-6201
Brain Neoplasms
Urea, Nitroso-, 79-6201
Calcium
Acetic Acid, (Ethylenebis(oxy-
thylene)nitro)tetra-, 79-6164
Adenosine Cyclic 3',5' Monophos-
phate, 79-6164
Adrenergic Beta Receptor Agonists
79-6164
Glucuronidase
Enzymatic Activity, 79-6201
Norepinephrine
Adenosine Cyclic 3',5' Monophos-
phate, 79-6164
Nucleic Acids
Amino Acids, 79-6201
Spinal Cord Neoplasms
Urea, Ethyl Nitroso-, 79-6210
Urea, Nitroso-
Nucleic Acids, 79-6201

Glucocorticoids
Bladder Neoplasms
Receptors, Hormone, Review, 79-6095

Glucose
Carcinoma, Ehrlich Tumor
Karyotyping, 79-6536

Glucosephosphatase
Carbon Tetrachloride
Liver, Rat, 79-6147
Isopropyl Alcohol
Liver, Rat, 79-6147
Methanol
Liver, Rat, 79-6147

Glucuronidase
Benzo(a)pyrene
Quinone Metabolites, 79-6325
Glioma
Enzymatic Activity, 79-6201
Intestinal Neoplasms
Pectin, 79-6176

Glutamyl Transpeptidase
Hepatoma
Benzenamine, 2-Methyl-4-((2-
methylphenyl)azo)-, 79-6234
Liver Neoplasms
Precancerous Conditions, 79-6194

Glutathione
Acetanilide, 4'-Hydroxy-
Hepatotoxic Metabolite, Review
79-6007
p-Acetophenetidine
Hepatotoxic Metabolite, Review
79-6007
Benzo(a)pyrene
Mutagenic Metabolite, 79-6323
Carbon Tetrachloride
Metabolism, 79-6149
Cobalt Chloride
Gastrointestinal System, 79-6219
Disulfide, Bis(dimethylthiocarbamoyl)-
Mutagenic Activity, 79-6199
Ethane, 1,2-Dibromo-
Carcinogenic Activity, 79-6150
Maleic Acid, Diethyl Ester
Gastrointestinal System, 79-6219
Stomach Neoplasms

Glutathione (cont'd)
 Carcinogenic Metabolite, 79-6219
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-6219

Glycine, N,N-Bis(carboxymethyl)-
 Environmental Hazard
 Risk Evaluation, Canada, Review
 79-6107

Glycoproteins
 Fibrosarcoma
 Tumorigenic Clone Cells, 79-6596
 Melanoma
 Neoplasm Metastasis, 79-6534
 Membrane Proteins
 Neoplasm Metastasis, 79-6534
 Phorbol Esters
 Cell Membrane, 79-6267
 Fibroblasts, 79-6267
 Virus, Avian Sarcoma
 RNA, Messenger, 79-6380
 Virus, Rous Sarcoma
 Binding Sites, 79-6390
 Fibroblasts, 79-6390

Glycosaminoglycans
 Virus, Rous Sarcoma
 Cell Transformation, Neoplastic
 79-6389

Glyoxal
 Ames Test
 Mutagenic Activity, 79-6160

Gold
 Lung Neoplasms
 Occupational Hazard, 79-6585
 Silicosis
 Occupational Hazard, 79-6585

Gonadotropins
 Leydig Cell Tumor
 Parabiosis, 79-6351

Graft vs Host Reaction
 Lymphoma
 Morphological Study, Mouse, 79-6485
 Lymphosarcoma
 Virus, Epstein-Barr, 79-6429
 Pregnancy
 Immunogenetics, 79-6485
 Sarcoma, Reticulum Cell
 Morphological Study, Mouse, 79-6485

Granuloma
 Hodgkin's Disease
 Histological Study, 79-6521
 Lymphosarcoma
 Histological Study, 79-6521
 T-Lymphocytes, 79-6521
 Sarcoma, Reticulum Cell
 Histological Study, 79-6521

Growth Substances
 Cell Transformation, Neoplastic
 Horse Serum, 79-6129
 Chromosome Aberrations
 Horse Serum, 79-6129
 Virus, Rous Sarcoma
 Cell Cycle Kinetics, 79-6387
 Temperature Sensitive Mutants
 79-6387

Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Adenocarcinoma
 Age Factors, Rat, 79-6223
 Cells, Cultured, 79-6220
 Precancerous Conditions, 79-6221
 Arginine
 Chromosome Aberrations, 79-6224
 Carcinoma, Epidermoid
 Cells, Cultured, 79-6220
 Cell Transformation, Neoplastic
 Trachea, Rat, 79-6220
 Chromatids
 Cell Division, 79-6224
 DNA
 Antinuclear Factors, 79-6466
 T-Lymphocytes, 79-6466

Guanidine, 1-Methyl-3-nitro-1-nitroso-
 (cont'd)
 Gastric Mucosa
 Carcinogenic Activity, 79-6218
 Cell Membrane Permeability, 79-6218
 DNA Replication, 79-6222
 Ultrastructural Study, 79-6218
 Stomach Neoplasms
 Adenocarcinoma, 79-6221, 79-6222
 79-6223
 Adenoma, 79-6222
 Glutathione, 79-6219
 Precancerous Conditions, 79-6222

Guanine
 Benzo(a)pyrene
 DNA Adducts, 79-6324

Guanine, 7-Methyl-
 Acetamide, N-Fluoren-2-yl-
 DNA Repair, 79-6170
 Dimethylamine, N-Nitroso-
 DNA Adducts, 79-6315
 DNA, Alkylation, 79-6186
 DNA Repair, 79-6170

Guanosine Cyclic 3',5' Monophosphate
 Mesothelioma
 Asbestos, 79-6231

Gynecologic Neoplasms
 Adenocarcinoma
 Hemorrhage, 79-6551
 Metaplasia
 4,4'-Stilbenediol, α,α' -Diethyl-
 79-6342
 Polyps
 Hemorrhage, 79-6551
 Smoke Condensate
 Transplacental, Neonatal Carcinogene-
 sis, 79-6285
 4,4'-Stilbenediol, α,α' -Diethyl-
 Transplacental Carcinogenesis, Review
 79-6025
 4,4'-Stilbenediol, α,α' -Diethyl-
 Ultrastructural Study, Mouse, 79-6342
 Toxaphene
 Carcinogenic Potential, Review
 79-6003
 Mouse, Rat, Review, 79-6003

Hair Dyes
 Ames Test
 Mutagenic Activity, Review, 79-6046
 Carcinogen, Chemical
 Risk Factors, Review, 79-6062

Hamartoma
 Nephroblastoma
 Genetics, 79-6546
 Histological Study, 79-6545

Haptens
 T-Lymphocytes
 Lymphocytotoxicity, Review, 79-6082

Harman
 Benzo(a)pyrene
 Co-carcinogenic Effect, Review
 79-6016

HeLa Cells
 Urea, Methyl Nitroso-
 DNA Repair, 79-6466

Hemagglutination
 Intestinal Neoplasms
 Isoantigens, 79-6513

Hemangioendothelioma
 Dimethylamine, N-Nitroso-
 Dose-Response Study, Rat, 79-6188

Hematopoietic Stem Cells
 Leukemia, Myeloblastic
 Colony Formation, Review, 79-6090
 Virus, Radiation Leukemia
 Virus Cultivation, 79-6399

Hemoglobins
 Ethylene Oxide

Hemoglobins (cont'd)
 Alkylation, Review, 79-6049

Hemolysis
 Sarcoma
 Isoantibodies, 79-6500

Hemorrhage
 Breast Neoplasms
 Gastritis, 79-6550
 Gastritis
 Antineoplastic Agents, 79-6550
 Corticosteroids, 79-6550
 Salicylic Acid, 79-6550
 Gynecologic Neoplasms
 Adenocarcinoma, 79-6551
 Polyps, 79-6551
 Leukemia
 Peptic Ulcer, 79-6550
 Lymphoma
 Peptic Ulcer, 79-6550
 Peptic Ulcer
 Salicylic Acid, 79-6550

Hepatitis
 Leukemia
 Azathioprine, 79-6255

Hepatosarcoma
 Acetamide, N-Fluoren-2-yl-
 Alpha Fetoproteins, 79-6172
 Neoplasm Transplantation, 79-6172
 Aflatoxin B1
 Corn Oil, 79-6279
 Dietary Fats, 79-6279
 Albumins
 Cells, Cultured, 79-6597
 Alpha 1-Antitrypsin
 Alpha Fetoproteins, 79-6542
 Immunohistochemical Study, 79-6542
 Alpha Fetoproteins
 Cells, Cultured, 79-6597
 Precancerous Conditions, 79-6234
 Amino Acids
 Biological Transport, 79-6598
 Aniline, N,N-Dimethyl-p-phenylazo-
 Antigens, Neoplasm, 79-6310
 Immune Serums, 79-6507
 Aniline, N-Methyl-p-(phenylazo)-
 Barbituric Acid, 5-Ethyl-5-phenyl-
 79-6246
 Anthraquinone, 2-Amino-
 Carcinogenic Activity, Mouse, 79-6262
 Diet, 79-6262
 Anthraquinone, 1-Amino-2-methyl-
 Carcinogenic Activity, Rat, 79-6262
 Anthraquinone, 2-Methyl-1-nitro-
 Carcinogenic Activity, Mouse, 79-6262
 Antigens, Neoplasm
 Isolation and Characterization
 79-6310
 Australia Antigen
 Immunologic Technics, 79-6543
 Isolation and Characterization
 79-6462
 Peptides, 79-6462
 Benzenamine, 2-Methyl-4-((2-
 methylphenyl)azo)-
 Alpha Fetoproteins, 79-6234
 Glutamyl Transpeptidase, 79-6234
 Carcinogen, Chemical
 Alpha Fetoproteins, Review, 79-6038
 Chromosomal Proteins, Non-Histone,
 Review, 79-6038
 Chlordane
 Alpha Fetoproteins, 79-6172
 Neoplasm Transplantation, 79-6172
 Cholesterol, 14-Methylhexadecanoate
 Metabolism, 79-6338
 Complement
 Antibody-Dependent Cell Cytotoxicity
 79-6507
 Growth, 79-6507
 Contraceptives, Oral
 Epidemiology, 79-6574
 Dextrans
 Endocytosis, 79-6229
 Diethylamine, N-Nitroso-

Hepatoma (cont'd)

- Dose-Response Study, 79-6193
- Hemeostasis, 79-6193
- Neoplasm Metastasis, 79-6195
- Dimethylamine, *N*-Nitroso-
 - Cell Cycle Kinetics, 79-6186
 - DNA, Alkylation, 79-6186
 - Dose-Response Study, Rat, 79-6188
- DNA, Binding
 - Molecular Biology, Review, 79-6001
- Histocompatibility Antigens
 - Lymphocyte Microcytotoxicity Assay, 79-6506
- Hydrocarbons, Chlorinated
 - Histological Study, 79-6259
- Hydrocarbons, Halogenated
 - Precancerous Conditions, Review, 79-6005
- Aniline, *N,N*-Methyl-*p*-(phenylazo)-, Hydroxy-
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-6246
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
 - Dose-Response Study, Rat, 79-6216
- Isobutyric Acid, α -Amino-
 - Amino Acids, 79-6598
- Lysosomes
 - Cell Cycle Kinetics, 79-6229
- Neoplasm Metastasis
 - Mouse, 79-6541
- Nephritis, Interstitial
 - Diet, 79-6262
- Peroxidases
 - Endocytosis, 79-6229
- Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester
 - Carcinogenic Activity, Rat, 79-6154
- Sarcoma, 79-6153
- Quinoline, 7-Chloro-4-((4-diethylamino)-1-methylbutyl)amino-
 - Endocytosis, 79-6229
- Sodium
 - Amino Acids, 79-6598
- Toluene-2,4-diamine
 - Histological Study, Mouse, 79-6240
 - Precancerous Conditions, 79-6240
- Transferrin
 - Cells, Cultured, 79-6597
- Virus, Hepatitis
 - Australia Antigen, 79-6506
 - Epidemiology, Review, 79-6080
 - Histocompatibility Antigens, 79-6506

Heptachlor

- Diet
 - Hepatocarcinogenesis, 79-6259

Hereditary Diseases

- Gastrointestinal Neoplasms
- Epidemiology, Review, 79-6100

2,5-Hexadienoic Acid, 3-Methoxy-5-methyl-4-oxo-

- RNA Polymerase
- RNA Replication, 79-6257

Histiocytes

- Breast Neoplasms
 - Lymph Nodes, 79-6548
- Neoplasm Metastasis, 79-6548
- Prognosis, 79-6548

Histocompatibility Antigens

- Autoimmune Diseases
 - Antigenic Determinants, Review, 79-6084
- Fibrosarcoma
 - Antigen-Antibody Reactions, 79-6494
 - Lymphocyte Cooperation, 79-6494
 - T-Lymphocytes, 79-6494
- Hepatoma
 - Lymphocyte Microcytotoxicity Assay, 79-6506
 - Virus, Hepatitis, 79-6506
- Immunization
 - Paraformaldehyde Fixation, 79-6509
- Joint Diseases
 - Antigenic Determinants, Review

Histocompatibility Antigens (cont'd)

- Antigenic Determinants, Review, 79-6084
- Leukemia
 - Antibody Specificity, 79-6477
 - Cell Membrane, 79-6477
 - Virus, AKR Murine Leukemia, 79-6477
- Leukemia, Lymphoblastic
 - Antigenic Determinants, Review, 79-6084
- Leukemia, Lymphocytic
 - B-Lymphocytes, 79-6472
 - B-Lymphocytes
 - Immune Response, Review, 79-6084
 - T-Lymphocytes
 - Lymphocytotoxicity, Review, 79-6082
- Lymphoma
 - Cholanthrene, 3-Methyl-, 79-6484
 - Radiation, 79-6484
- Mammary Neoplasms, Experimental
 - Immune Response, 79-6515
 - Transplantation Immunology, 79-6514
- Monocytes
 - Immune Response, Review, 79-6084
- Neoplasms, Experimental
 - Virus, SV40, 79-6509
- Nephroblastoma
 - Antigen Frequency, 79-6510
- Neuroblastoma
 - Antigen Frequency, 79-6510
- Virus, Murine Leukemia
 - Virus Replication, 79-6405
- Virus, Rous Sarcoma
 - Immunogenetics, 79-6498
 - Transplantation Immunology, 79-6498
- Virus, SV40
 - Antigens, Neoplasm, 79-6076
 - Transplantation Immunology, 79-6448

Histones

- Virus, SV40
 - Acetylation, 79-6600

Hodgkin's Disease

- Child
 - Epidemiology, Iran, 79-6589
- Granuloma
 - Histological Study, 79-6521
- Thyroid Neoplasms
 - Radiotherapy, 79-6369

Hyaluronic Acid

- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 79-6389

Hyaluronidase

- Virus, Polyoma
 - Cell Division, 79-6435

Hybrid Cells

- T-Lymphocytes
 - Immunogenetics, 79-6468
- Virus, Baboon C-Type RNA Tumor
 - Virus Replication, 79-6421, 79-6422
- Virus, Murine Mammary Tumor
 - DNA-DNA Hybridization, 79-6394
- Virus, SV40
 - RNA, Ribosomal, 79-6449

Hydrazine

- Copper
 - DNA Repair, 79-6141
- Iron
 - DNA Repair, 79-6141
- Manganese
 - DNA Repair, 79-6141
 - Structure-Activity Relationship, Ames Test, Review, 79-6023

Hydrazine, 1,2-Dimethyl-

- Adenocarcinoma
 - Nucleoproteins, 79-6177
 - Pectin, 79-6176
- Bacillus subtilis*
 - Mutagenic Activity, 79-6174
- Colonic Neoplasms
 - Adenocarcinoma, 79-6177

Hydrazine, 1,2-Dimethyl- (cont'd)

- DNA, Bacterial
 - Transforming Activity, 79-6174
- Intestinal Neoplasms
 - Adenocarcinoma, 79-6175, 79-6176
 - Adenoma, 79-6176
 - Carcinoma In Situ, 79-6175
 - Dietary Fiber, 79-6176
 - Precancerous Conditions, 79-6175

Hydrazine, Methyl-

- p*-Toluidide, *N*-Isopropyl- α -(2-methylhydrazino)-
 - Microsomes, Liver, 79-6244

Hydrocarbons, Chlorinated

- Cholangioma
 - Histological Study, 79-6259
- Hepatoma
 - Histological Study, 79-6259
- Liver Neoplasms
 - Diet, 79-6259
- Structure-Activity Relationship
 - Ames Test, Review, 79-6023

Hydrocarbons, Halogenated

- Hepatoma
 - Precancerous Conditions, Review, 79-6005

Hydroxylamine, *O*-Benzoyl-*N*-methyl-*N*-(*p*-(phenylazo)phenyl)-

- Sarcoma
 - Carcinogenic Activity, Rat, 79-6246

Hydroxylamine, *N*-methyl-*N*-(*p*-(phenylazo)phenyl)-

- Hepatoma
 - Barbituric Acid, 5-Ethyl-5-phenyl-, 79-6246
- Stomach Neoplasms
 - Carcinoma, 79-6246
- Papilloma, 79-6246

Hypercalcemia

- Carcinoma, Epidermoid
 - Arsenious Acid, Potassium Salt, 79-6132

Hyperplasia

- Adrenal Gland Neoplasms
 - Smoke Condensate, 79-6285
- Bladder Neoplasms
 - Cell Division, Review, 79-6095
- Carbon Tetrachloride
 - Pulmonary Alveoli, 79-6207
- Cholanthrene, 3-Methyl-
 - Pulmonary Alveoli, 79-6207
- Ethylene, Trichloro-
 - Pulmonary Alveoli, 79-6207
- Intestinal Mucosa
 - Surgery, Operative, 79-6378
- Liver Neoplasms
 - Dimethylamine, *N*-Nitroso-, 79-6188
 - Smoke Condensate, 79-6285
- Mammary Neoplasms, Experimental
 - Estradiol, 17-Ethynyl-, 79-6350
 - Megestrol Acetate, 79-6350
 - Mestranol, 79-6350
 - Neoplasm Transplantation, 79-6515
- Polychlorobiphenyl Compounds
 - Dermatologic Effects, Review, 79-6112
- Prostatic Neoplasms
 - Histopathological Diagnosis, 79-6553
- Uterine Neoplasms
 - Precancerous Conditions, Review, 79-6124

Hypersensitivity, Delayed

- Fibrosarcoma
 - Neoplasm Transplantation, 79-6495
- Mouth Neoplasms
 - Benzene, 1-Chloro-2,4-dinitro-, 79-6298

Hypertension

- Uterine Neoplasms
 - Epidemiology, Israel, 79-6567

Hypothyroidism
 Fibrosarcoma
 Neoplasm Metastasis, 79-6595
 Sarcoma
 Neoplasm Metastasis, 79-6595

Hysterectomy
 Ovarian Neoplasms
 Epidemiology, Review, 79-6120

IgA
 Multiple Myeloma
 Asbestos, 79-6133
 Plasmacytoma
 Anti-Antibodies, 79-6489

IgD
 Leukemia, Lymphocytic
 Immunoglobulins, Light Chain
 79-6472

IgG
 Adenoma
 Antigen-Antibody Complex, 79-6505
 Chordoma
 Antigen-Antibody Complex, 79-6505
 Fibrosarcoma
 Isoantibodies, 79-6496
 Leukemia, Hairy Cell
 Receptors, Fc, 79-6525
 Melanoma
 Antigen-Antibody Complex, 79-6505
 Multiple Myeloma
 Asbestos, 79-6133
 Plasmacytoma
 Amyloid, 79-6492
 Virus, Avian Sarcoma
 Phosphorylation, 79-6383
 Virus, SV40
 T-Lymphocytes, 79-6448

IgM
 Leukemia, Lymphocytic
 B-Lymphocytes, 79-6471

Imidazole-1-ethanol, 2-Methyl-5-nitro-
 Cervix Neoplasms
 Carcinoma In Situ, 79-6217
 Hepatoma
 Dose-Response Study, Rat, 79-6216
 Lung Neoplasms
 Risk Factors, 79-6217
 Mammary Neoplasms, Experimental
 Dose-Response Study, Rat, 79-6216
 Pituitary Neoplasms
 Adenoma, 79-6216
 Smoking
 Co-carcinogenic Effect, 79-6217
 Testicular Neoplasms
 Leydig Cell Tumor, 79-6216
 Vaginal Preparations
 Carcinogenic Potential, Review
 79-6055

Imidazole-2-thiol, 1-Methyl-
 Ethane, 1,2-Dibromo-
 Carcinogenic Activity, 79-6150

Immune Serums
 Hepatoma
 Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 79-6507
 Intestinal Neoplasms
 Complement, 79-6513
 Leukemia, Lymphoblastic
 Chemotaxis, 79-6474
 Leukemia, Lymphocytic
 T-Lymphocytes, 79-6470
 T-Lymphocytes
 Lymphocyte Cooperation, 79-6470
 Lymphocyte Culture Test, Mixed
 79-6470
 Suppressor Cells, 79-6470
 Virus, Abelson Murine Leukemia
 Antigen-Antibody Reactions, 79-6403
 Virus, Rat Leukemia
 Cell Transformation, Neoplastic
 79-6412
 Virus, SV40

Immune Serums (cont'd)
 Lymphocyte Transformation, 79-6448

Immunity, Cellular
 Carcinoma, Ehrlich Tumor
 Trypan Blue, 79-6488
 Esophageal Neoplasms
 Carcinoma, Epidermoid, 79-6511
 Fibrosarcoma
 Ultraviolet Rays, 79-6494
 Leukemia, Radiation-Induced
 T-Lymphocytes, 79-6483
 T-Lymphocytes
 Lymphocyte Depletion, 79-6468
 Lymphoma
 T-Lymphocytes, 79-6468, 79-6484
 Virus, Moloney Murine Leukemia
 79-6486
 Virus, Adeno 2
 T-Lymphocytes, 79-6501
 Virus, Friend Spleen Focus-Forming
 Antigens, 79-6407

Immunity, Passive
 Lymphoma
 Virus, Rauscher Murine Leukemia
 79-6486
 Neoplasms, Experimental
 Mouse, Review, 79-6086

Immunization
 Histocompatibility Antigens
 Paraformaldehyde Fixation, 79-6509
 Leukemia L1210
 Virus, Sendai, 79-6479

Immunoglobulins, Fc
 Fibrosarcoma
 Isoantibodies, 79-6496

Immunoglobulins, Light Chain
 Leukemia, Lymphocytic
 IgD, 79-6472
 B-Lymphocytes, 79-6469, 79-6471
 Myeloma Proteins
 Idiotypic Determinants, 79-6503
 Plasmacytoma
 Chromosomes, 79-6491
 DNA, 79-6491

Immunoglobulins, Surface
 Leukemia, Hairy Cell
 B-Lymphocytes, 79-6482
 Leukemia, Lymphocytic
 B-Lymphocytes, 79-6472

Immunologic Deficiency Syndromes
 Skin Neoplasms
 Chromosome Aberrations, Review
 79-6092
 Radiation, Ionizing, 79-6092
 Ultraviolet Rays, 79-6092

Immunosuppression
 Erythroleukemia
 Virus, Friend Murine Leukemia
 79-6408
 Leukemia, Myelocytic
 Transplantation, Homologous, 79-6009
 Lymphoma
 Transplantation, Homologous, 79-6009
 Neoplasms
 Aging, Review, 79-6088
 Tumor Dormancy, Review, 79-6088
 Sarcoma, Reticulum Cell
 Antilymphocyte Serum, 79-6009
 Azathioprine, 79-6009
 Cyclophosphamide, 79-6009
 Transplantation, Homologous, 79-6009
 Virus, Friend Murine Leukemia
 Radiation, Ionizing, 79-6408
 Virus, SV40
 T-Lymphocytes, 79-6448

Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-
 5-methoxy-2-methyl-
 5,8,11-14-Eicosatetraenoic Acid
 Platelet Aggregation, 79-6272
 12-*O*-Tetradecanoylphorbol-13-acetate
 Prostaglandins, 79-6277

Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-
 5-methoxy-2-methyl- (cont'd)
 Prostaglandins E, 79-6274

Indole-3-acetic Acid, 5-Hydroxy-
 Prostatic Neoplasms
 Cholanthrene, 3-Methyl-, 79-6307

Interferon
 Carcinoma 256, Walker
 Growth, 79-6463
Clostridium welchii
 Toxicity, 79-6463
 Mycoplasma
 Toxicity, 79-6463
Salmonella typhimurium
 Toxicity, 79-6463

Intestinal Mucosa
 Hyperplasia
 Surgery, Operative, 79-6378

Intestinal Neoplasms
 Adenocarcinoma
 Hydrazine, 1,2-Dimethyl-, 79-6175
 79-6176
 Polyps, 79-6175
 Adenoma
 Hydrazine, 1,2-Dimethyl-, 79-6176
 Breast Neoplasms
 Epidemiology, 79-6558
 Carcinoid Tumor
 Epidemiology, India, 79-6582
 Carcinoma In Situ
 Hydrazine, 1,2-Dimethyl-, 79-6175
 Precancerous Conditions, 79-6175
 Colitis, Ulcerative
 Precancerous Conditions, 79-6558
 Complement
 Immune Serums, 79-6513
 Dietary Fats
 Epidemiology, Review, 79-6114
 Dietary Fiber
 Epidemiology, Britain, 79-6559
 Pentoses, 79-6559
 Glucuronidase
 Pectin, 79-6176
 Hydrazine, 1,2-Dimethyl-
 Dietary Fiber, 79-6176
 Precancerous Conditions, 79-6175
 Isoantigens
 Antibody Specificity, 79-6513
 Hemagglutination, 79-6513
 Leiomyoma
 Propionic Acid, 2-(*p*-Chlorophenoxy)-
 2-methyl-, Ethyl Ester, 79-6154
 Methane, Azoxy-
 Surgery, Operative, 79-6378
 Precancerous Conditions
 Histological Study, 79-6175
 Surgery, Operative
 Enterectomy, 79-6378
 Urogenital Neoplasms
 Epidemiology, 79-6558

Iron
 Hydrazine
 DNA Repair, 79-6141
 Occupational Hazard
 Epidemiology, Review, 79-6054

Islet Cell Tumor
 Pancreatic Neoplasms
 Strain Difference, Hamster, 79-6544

Isoantibodies
 Fibrosarcoma
 Growth, 79-6496
 IgG, 79-6496
 Immunoglobulins, Fc, 79-6496
 Sarcoma
 Hemolysis, 79-6500

Isoantigens
 Intestinal Neoplasms
 Antibody Specificity, 79-6513
 Hemagglutination, 79-6513
 T-Lymphocytes
 Antigen-Antibody Reactions, 79-6470

- Isobutyric Acid, α -Amino-**
Amino Acids
Liver, Rat, 79-6598
Hepatoma
Amino Acids, 79-6598
- Isonicotinic Acid,**
2-(2-(Benzylcarbamoyl)ethyl)hydrazide
Manganese
DNA Repair, 79-6141
- Isonicotinic Acid Hydrazide**
Catalase
DNA Repair, 79-6141
DNA Repair
Fibroblasts, 79-6141
Manganese
DNA Repair, 79-6141
- Isonicotinic Acid, 2-Isopropylhydrazide**
Manganese
DNA Repair, 79-6141
- Isopropyl Alcohol**
Alanine Aminotransferase
Serum Levels, 79-6147
Carbon Tetrachloride
Hepatotoxicity, 79-6147
Glucosephosphatase
Liver, Rat, 79-6147
Triglycerides
Liver, Rat, 79-6147
- Jaw Neoplasms**
Burkitt's Lymphoma
Nonendemic Disease, 79-6524
- Joint Diseases**
Histocompatibility Antigens
Antigenic Determinants, Review
79-6084
- Karyotyping**
Carcinoma, Ehrlich Tumor
Glucose, 79-6536
Succinic Acid, Disodium Salt, 79-6536
Leukemia, Myeloblastic
Chromosomes, Human, 21-22, 79-6522
- Keponc**
Adrenal Cortex
Carcinogenic Potential, Review
79-6005
Diet
Hepatocarcinogenesis, 79-6259
Porphyria
Hepatocarcinogenesis, Review
79-6005
- Keratinosis, Sublingual**
see Leukoplakia, Oral
- Kidney Neoplasms**
Adenocarcinoma
Anthraquinone, 1-Amino-2-methyl-
79-6262
Alkylating Agents
DNA Repair, Review, 79-6065
Asbestos
Epidemiology, Review, 79-6052
Morpholine, *N*-Nitroso-
Precancerous Conditions, 79-6215
- Kinases**
see Phosphotransferases, ATP
- Kojic Acid**
see 4*H*-Pyran-4-one, 5-Hydroxy-
2-(hydroxymethyl)-
- Lactate Dehydrogenase**
Aflatoxin B1
Dietary Proteins, 79-6280
Precancerous Conditions, 79-6280
Dimethylamine, *N*-Nitroso-
Cell Membrane Permeability, 79-6192
Dimethylamine, *N*-Nitroso-
Cell Membrane Permeability, 79-6192
Sebaceous Gland Neoplasms
Zymbal Gland, Rat, 79-6302
- Lactation**
Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor
79-6398
Virus, Murine Mammary Tumor
Antigens, Viral, 79-6396
- Lactic Acid**
4,4'-Bipyridinium, 1,1'-Dimethyl-, Di-
chloride
Lung, Mouse, 79-6187
Dimethylamine, *N*-Nitroso-
Lung, Mouse, 79-6187
Lung Neoplasms
Carbamic Acid, Ethyl Ester, 79-6187
Dimethylamine, *N*-Nitroso-, 79-6187
Phenol, (1,1-Dimethylethyl)-4-
methoxy-, 79-6187
Precancerous Conditions, 79-6187
- Lactose**
Lymphoma
Cell Aggregation, 79-6593
- Laminaran**
Leukemia L1210
Immune Response, 79-6478
- Laryngeal Neoplasms**
Carcinoma
Smoking, 79-6284
Smoking
Inhalation Study, Hamster, 79-6284
Tobacco Substitutes, 79-6284
- Lead**
Air Pollution
Toxicity, Review, 79-6105
Occupational Hazard
Epidemiology, Review, 79-6054
Water Pollution
Risk Factors, Review, 79-6109
- Leiomyoma**
Intestinal Neoplasms
Propionic Acid, 2-(*p*-Chlorophenoxy)-
2-methyl-, Ethyl Ester, 79-6154
- Leukemia**
Ataxia Telangiectasia
DNA Repair, Review, 79-6067
Azathioprine
Case Report, 79-6255
Hepatitis, 79-6255
Carcinogen, Chemical
Dietary Proteins, Review, 79-6041
Histocompatibility Antigens
Antibody Specificity, 79-6477
Cell Membrane, 79-6477
Neoplasm Metastasis
Mouse, 79-6541
Peptic Ulcer
Hemorrhage, 79-6550
Polish Migrants
England, Wales, 79-6557
Radiation, Ionizing
DNA, 79-6591
In Utero Exposure, Review, 79-6069
Virus, AKR Murine Leukemia
Histocompatibility Antigens, 79-6477
- Leukemia, Hairy Cell**
Acid Phosphatase
Diagnosis, 79-6482
IgG
Receptors, Fc, 79-6525
Lipopolysaccharides
Lymphocytes, 79-6481
B-Lymphocytes
Antibody Specificity, 79-6480
Immunoglobulins, Surface, 79-6482
Muramidase, 79-6480
Receptors, Fc, 79-6525
Monocytes
Antibody Specificity, 79-6480
Phagocytosis, 79-6482
Phagocytosis
Acid Phosphatase, 79-6525
- Leukemia L1210**
BCG
Immune Response, 79-6478
Laminaran
Immune Response, 79-6478
Pyran Copolymer
Drug Therapy, 79-6478
Vaccine Potentiation, 79-6478
Virus, Sendai
Immunization, 79-6479
Transplantation Immunology, 79-6479
- Leukemia, Lymphoblastic**
Chemotaxis
Immune Serums, 79-6474
Inhibitory Factor, 79-6474
Histocompatibility Antigens
Antigenic Determinants, Review
79-6084
B-Lymphocytes
Precursor Cells, 79-6475
T-Lymphocytes
Precursor Cells, 79-6475
Null Cells
Lymphocyte Culture Test, Mixed
79-6475
- Leukemia, Lymphocytic**
Asbestosis
Case Report, 79-6133
Benz(a)anthracene, 7,12-Dimethyl-
Phorbol, 79-6299
Carcinoma, Basal Cell
Case Report, 79-6473
Carcinoma, Epidermoid
Case Report, 79-6473
IgD
Immunoglobulins, Light Chain
79-6472
Lipopolysaccharides
DNA Replication, 79-6471
B-Lymphocytes
Ethanol, 2-Mercapto-, 79-6471
Histocompatibility Antigens, 79-6472
IgM, 79-6471
Immunoglobulins, Light Chain
79-6469, 79-6471
Immunoglobulins, Surface, 79-6472
Receptors, FC, 79-6472
T-Lymphocytes
Immune Serums, 79-6470
Phorbol
Carcinogenic Activity, Mouse, 79-6189
Dimethylamine, *N*-Nitroso-, 79-6189
Radiation, Ionizing
Mouse, NBZ, 79-6366
Virus, Murine Leukemia, 79-6366
Spleen
Neoplasm Circulating Cells, 79-6469
- Leukemia, Myeloblastic**
Alanine, 3-(*p*-(Bis(2-
chloroethyl)amino)phenyl)-
Drug Therapy, 79-6009
BCG
Immunologic Technics, 79-6476
1,4-Butanediol, Dimethylsulfonate
Drug Therapy, 79-6009
Carcinoma Epidermoid
Case Report, 79-6520
Chromosomes, Human, 21-22
Immune Response, 79-6522
Karyotyping, 79-6522
Cyclophosphamide
Drug Therapy, 79-6009
Hematopoietic Stem Cells
Colony Formation, Review, 79-6090
Lymphocytes
Cytotoxic Effector Cells, 79-6476
Skin Neoplasms
Carcinoma Epidermoid, 79-6520
- Leukemia, Myelocytic**
Arginine
Blastic Crises, 79-6592
Metabolism, 79-6592
Immunosuppression
Transplantation, Homologous, 79-6009

Leukemia, Myelocytic (cont'd)
 Radiation, Ionizing
 Chromosome Aberrations, 79-6367
 Occupational Hazard, 79-6576

Leukemia, Radiation-Induced
 T-Lymphocytes
 Antigen-Antibody Reactions, 79-6483
 Immunity, Cellular, 79-6483
 Radiation, Ionizing
 T-Lymphocytes, 79-6483

Leukocytes
 Lymphosarcoma
 Fetal Blood, 79-6429

Leukoplakia, Oral
 Mouth Neoplasms
 Carcinoma, 79-6531
 Smoking, 79-6531

Leydig Cell Tumor
 Gonadotropins
 Parabiosis, 79-6351
 Testicular Neoplasms
 FSH, 79-6351
 Imidazole-1-ethanol, 2-Methyl-5-nitro-
 79-6216
 LH, 79-6351

LH
 Testicular Neoplasms
 Leydig Cell Tumor, 79-6351
 Uterine Neoplasms
 Adenocarcinoma, 79-6552

Light
 Benz(a)anthracene-7,12-dione
 Photooxidation Product, 79-6290
 Benz(a)anthracene-7-carboxaldehyde, 12-Methyl-
 Photooxidation Product, 79-6290
 Benz(a)anthracene-12-carboxaldehyde, 7-Methyl-
 Photooxidation Product, 79-6290
 Benz(a)anthracene-7-methanol, 12-Methyl-
 Photooxidation Product, 79-6290
 Benz(a)anthracene-12-methanol, 7-Methyl-
 Photooxidation Product, 79-6290
 Carcinomas
 Acridine, 3,6-Diamino-, 79-6287
 Psoralen, 8-Methoxy-, 79-6287

Lymphoma
 Acridine, 3,6-Diamino-, 79-6287
 Neutral Red, 79-6287
 Mammary Neoplasms, Experimental
 Acridine, 3,6-Diamino-, 79-6287
 Neutral Red, 79-6287
 Skin Neoplasms
 Acridine, 3,6-Diamino-, 79-6287
 Neutral Red, 79-6287
 Thyroid Neoplasms
 Neutral Red, 79-6287

Linoleic Acid, Methyl Ester
 Nitrous Acid, Sodium Salt
 Reaction Products, 79-6179

Lipids
 Nitrosamines
 Nitrous Acid, Sodium Salt, 79-6179

Lipoma
 Spinal Cord Neoplasms
 Cauda Equina, 79-6555
 Epidemiology, Child, 79-6555

Lipoplysaccharides
 Aryl Hydrocarbon Hydroxylases
 B-Lymphocytes, 79-6296
 Leukemia, Hairy Cell
 Lymphocytes, 79-6481
 Leukemia, Lymphocytic
 DNA Replication, 79-6471

Lipoproteins
 Aniline, *N,N*-Dimethyl-*p*-phenylazo-
 Binding, 79-6247

Liver
 Aniline, *N*-Methyl-*p*-(phenylazo)-
 Binding, 79-6237
 Aniline, *p*-(Phenylazo)-
 Binding, 79-6237
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 Binding, 79-6237
p-Phenylenediamine
 Binding, 79-6237

Liver Cirrhosis
 Australia Antigen
 Immunologic Technics, 79-6543

Liver Neoplasms
 Acetamide, *N,N'*-Fluorene-2,7-diylbis-
 Histochemical Study, Peroxisomes
 79-6171
 Precancerous Conditions, 79-6171

Adenoma
 Phorbol, 79-6189
 4 α -Phorbol, 79-6189
 Phorbol, 12-Deoxy-, 79-6189

Aflatoxin B1
 Precancerous Conditions, 79-6280
 Aniline, *N*-Ethyl-*p*-(phenylazo)-
 Hydroxy Derivative, 79-6246
 Aniline, *p*-(Phenylazo)-
 Hydroxy Derivative, 79-6246
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Carcinogenic Potential, Review
 79-6047

Diethylamine, *N*-Nitroso-
 Choline, 79-6194
 Precancerous Conditions, 79-6194

Dimethylamine, *N*-Nitroso-
 Phorbol, 79-6189
 Phorbol Esters, 79-6189

Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 Carcinogenic Potential, Review
 79-6047

Glutamyl Transpeptidase
 Precancerous Conditions, 79-6194

Hydrocarbons, Chlorinated
 Diet, 79-6259

Hyperplasia
 Dimethylamine, *N*-Nitroso-, 79-6188
 Smoke Condensate, 79-6285

Morpholine, *N*-Nitroso-
 Precancerous Conditions, 79-6215

Mycotoxins
 Epidemiology, Review, 79-6099

Phorbol
 Transplacental Carcinogenesis
 79-6266
 Tritium, 79-6266

Piper nigrum
 Carcinogenic Potential, 79-6258

Polychlorobiphenyl Compounds
 Carcinogenic Potential, Review
 79-6112

Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester
 Histochemical Study, Peroxisomes
 79-6171

Pyrethrum
 Carcinogenic Potential, Review
 79-6047

Smoke Condensate
 Transplacental, Neonatal Carcinogenesis, 79-6285

Toxaphene
 Mouse, Rat, Review, 79-6003

Urea, Methyl Nitroso-
 DNA Repair, Review, 79-6065

Virus, Hepatitis
 Epidemiology, Review, 79-6099

Liver Regeneration
 Dimethylamine, *N*-Nitroso-
 Cell Cycle Kinetics, 79-6186

Lung
 Americium
 Half-Life, 79-6375
 Fibrosarcoma
 Neoplasm Metastasis, 79-6493
 Plutonium
 Half-Life, 79-6373

Lung Neoplasms
Adenoma
 Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-, 79-6017
 Cholanthren-2-ol, 3-Methyl-, 79-6308
 Cholanthren-2-one, 3-Methyl-, 79-6308
 Cholanthren, 9,10-Dihydro-3-methyl-1,9,10-trihydroxy-, 79-6308
 Mouse, 79-6541
 Phorbol, 79-6266

Adenosine, Methyl Nitroso-
 Carcinogenic Activity, Mouse, 79-6232

Air Pollution
 Nickel, 79-6054

Arsenic
 Occupational Hazard, 79-6115

Asbestos
 Occupational Hazard, 79-6115

Benzo(a)pyrene
 Metabolism, 79-6331

Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
 Carcinogenic Metabolite, Review
 79-6017

1,3-Butadiene, 2-Chloro-
 Carcinogenic Potential, Review
 79-6050

Carbamic Acid, Ethyl Ester
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6110
 Lactic Acid, 79-6187
 Phosphotransferases, ATP, 79-6187

Carcinogen, Chemical
 Enzyme Activation, Review, 79-6102

Carcinoma, Epidermoid
 Bronchopulmonary Sequestration
 79-6537
 Case Report, 79-6537

Chromic Acid
 Occupational Hazard, 79-6115

Coal
 Occupational Hazard, 79-6585

Cyclophosphamide
 Neoplasm Metastasis, 79-6161

Diethylamine, *N*-Nitroso-
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6110

Dimethylamine, *N*-Nitroso-
 Lactic Acid, 79-6187
 Phosphotransferases, ATP, 79-6187

Environmental Hazard
 Asbestos, 79-6569

Ethnic Groups
 Epidemiology, Bombay, 79-6583

Gold
 Occupational Hazard, 79-6585

Imidazole-1-ethanol, 2-Methyl-5-nitro-
 Risk Factors, 79-6217

Lactic Acid
 Precancerous Conditions, 79-6187

Occupational Hazard
 Epidemiology, Review, 79-6053
 79-6054, 79-6115

Phenol, (1,1-Dimethylethyl)-4-methoxy-
 Lactic Acid, 79-6187

Phorbol
 Transplacental Carcinogenesis
 79-6266
 Tritium, 79-6266

Piper nigrum
 Carcinogenic Potential, 79-6258

Polish Migrants
 England, Wales, 79-6557

Radiation, Ionizing
 Occupational Hazard, 79-6576

Radon
 Dose-Response Study, 79-6371
 Epidemiology, 79-6371

Retinol
 Epidemiology, Review, 79-6026

Lung Neoplasms (cont'd)

- Sarcoma
 - Neoplasm Metastasis, 79-6534
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Smoking
 - Epidemiology, Australia, 79-6585
 - Epidemiology, Bombay, 79-6583
 - Epidemiology, Review, 79-6053
- Tars
 - Smoking, 79-6584
- Uranium
 - Occupational Hazard, 79-6371
- Virus, Herpes Simplex 2
 - Neoplasm Metastasis, 79-6532
- Virus, Murine Sarcoma
 - Neoplasm Metastasis, 79-6538

Lupus Erythematosus, Systemic

- Caffeine
 - DNA Repair, 79-6358

Luteoskyrin

- Ribonuclease
 - Enzyme Inhibition, 79-6257
- RNA Polymerase
 - RNA Replication, 79-6257

Lymph Nodes

- Breast Neoplasms
 - Histiocytes, 79-6548
 - Immune Response, 79-6549
 - T-Lymphocytes, 79-6549
 - Neoplasm Metastasis, 79-6549
- Burkitt's Lymphoma
 - Histological Study, 79-6523

Lymphangioma

- Abdominal Neoplasms
 - Radiation, Ionizing, 79-6370

Lymphangiosarcoma

- Abdominal Neoplasms
 - Neoplasm Recurrence, Local, 79-6370
- Carcinoma, Epidermoid
 - Radiotherapy, 79-6370

Lymphatic Diseases

- Virus, C-Type RNA Tumor
 - Cross-Species Transmission, 79-6461
 - Isolation and Characterization, Turkey, 79-6461

Lymphocyte Transformation

- Cervix Neoplasms
 - Virus, Herpes Simplex 1, 79-6426
 - Virus, Herpes Simplex 2, 79-6426
- Concanavalin A
 - Dietary Fats, 79-6516
 - DNA Replication, 79-6465
- Lymphocyte Transformation
 - Plant Agglutinins, 79-6465
- Plant Agglutinins
 - Lymphocyte Transformation, 79-6465
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Suppressor Cells, 79-6270
 - Ultrastructural Study, 79-6269
- Virus, Epstein-Barr
 - DNA, Viral, 79-6430
- Virus, Herpes Simplex 1
 - Antigens, Viral, 79-6426
- Virus, Herpes Simplex 2
 - Antigens, Viral, 79-6426
- Virus, SV40
 - Concanavalin A, 79-6448
 - Immune Serums, 79-6448
 - Plant Agglutinins, 79-6448

Lymphocytes

- Leukemia, Hairy Cell
 - Lipopolysaccharides, 79-6481
- Leukemia, Myeloblastic
 - Cytotoxic Effector Cells, 79-6476
- Methanesulfonic Acid, Methyl Ester
 - Chromatids, 79-6145
- Multiple Myeloma
 - Myeloma Proteins, 79-6503
- Platinum, Diamminedichloro-, *cis*-
 - Chromatids, 79-6143

Lymphocytes (cont'd)

- Psoralen, 8-Methoxy-
 - Chromatids, 79-6359
- Quinacrine
 - Chromatids, 79-6145
- Quinacrine Mustard
 - Chromatids, 79-6145
- Quinoline, 4-Nitro-, 1-Oxide
 - DNA Repair, 79-6358
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Agglutination, 79-6269
- Tritium
 - Chromatids, 79-6353
- Ultraviolet Rays
 - Chromatids, 79-6359
 - DNA Repair, 79-6358
- Uridine, 5-Bromo-2'-deoxy-
 - Chromatids, 79-6225

B-Lymphocytes

- Benz(a)anthracene
 - Aryl Hydrocarbon Hydroxylases, 79-6296, 79-6313
- Benzo(a)pyrene
 - Aryl Hydrocarbon Hydroxylases, 79-6313
 - Carcinogenic Metabolite, 79-6296
- Cholanthrene, 3-Methyl-
 - Aryl Hydrocarbon Hydroxylases, 79-6313
- Concanavalin A
 - Aryl Hydrocarbon Hydroxylases, 79-6296
- Dibenz(a,h)anthracene
 - Aryl Hydrocarbon Hydroxylases, 79-6296, 79-6313
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Aryl Hydrocarbon Hydroxylases, 79-6313
- Histocompatibility Antigens
 - Immune Response, Review, 79-6084
- Leukemia, Hairy Cell
 - Antibody Specificity, 79-6480
 - Immunoglobulins, Surface, 79-6482
 - Muramidase, 79-6480
 - Receptors, Fc, 79-6525
- Leukemia, Lymphoblastic
 - Precursor Cells, 79-6475
- Leukemia, Lymphocytic
 - Ethanol, 2-Mercapto-, 79-6471
 - Histocompatibility Antigens, 79-6472
 - IgM, 79-6471
 - Immunoglobulins, Light Chain, 79-6469, 79-6471
 - Immunoglobulins, Surface, 79-6472
 - Receptors, FC, 79-6472
- Lipopolysaccharides
 - Aryl Hydrocarbon Hydroxylases, 79-6296
- Lymphoma
 - Neoplasm Circulating Cells, 79-6469
- Oxazole, 2,5-Diphenyl-
 - Enzyme Inhibition, 79-6313
- Paraproteinemia
 - Lymphocyte Cooperation, 79-6467
- Plant Agglutinins
 - Aryl Hydrocarbon Hydroxylases, 79-6296
- Virus, Epstein-Barr
 - Chromosome Aberrations, Review, 79-6078
 - Lymphocyte Transformation, Review, 79-6078
- Virus, Herpes Gorilla
 - Cell Transformation, Neoplastic, 79-6424

T-Lymphocytes

- Adenocarcinoma
 - Antibody Formation, 79-6517
 - 79-6518
 - Hypersensitivity, 79-6517, 79-6518
 - Lymphocyte Depletion, 79-6517
 - 79-6518
 - Neoplasm Metastasis, 79-6517
- Alkylating Agents
 - Receptors, Fc, 79-6466

T-Lymphocytes (cont'd)

- Benz(a)anthracene, 7,12-Dimethyl-
 - Lymphocyte Transformation, Review, 79-6078
 - Breast Neoplasms
 - Lymph Nodes, 79-6549
 - Cyclophosphamide
 - DNA, 79-6466
 - Esophageal Neoplasms
 - Plant Agglutinins, 79-6511
 - Fibrosarcoma
 - Histocompatibility Antigens, 79-6494
 - Lymphocyte Depletion, 79-6493
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - DNA, 79-6466
 - Haptens
 - Lymphocytotoxicity, Review, 79-6082
 - Histocompatibility Antigens
 - Lymphocytotoxicity, Review, 79-6082
 - Hybrid Cells
 - Immunogenetics, 79-6468
 - Immune Serums
 - Lymphocyte Cooperation, 79-6470
 - Lymphocyte Culture Test, Mixed, 79-6470
 - Suppressor Cells, 79-6470
 - Isoantigens
 - Antigen-Antibody Reactions, 79-6470
 - Leukemia, Lymphoblastic
 - Precursor Cells, 79-6475
 - Leukemia, Lymphocytic
 - Immune Serums, 79-6470
 - Leukemia, Radiation-Induced
 - Antigen-Antibody Reactions, 79-6483
 - Immunity, Cellular, 79-6483
 - Radiation, Ionizing, 79-6483
 - Lymphocyte Depletion
 - Immunity, Cellular, 79-6468
 - Lymphoma
 - Immunity, Cellular, 79-6468, 79-6484
 - Lymphosarcoma
 - Granuloma, 79-6521
 - Methanesulfonic Acid, Methyl Ester
 - DNA, 79-6466
 - Paraproteinemia
 - Aging, 79-6467
 - Plasmacytoma
 - Cell Differentiation, 79-6489
 - Receptors, Fc, 79-6489
 - Radiation, Ionizing
 - Lymphocyte Transformation, Review, 79-6078
 - Macrophage Activation, 79-6468
 - Sarcoma
 - Cholanthrene, 3-Methyl-, 79-6502
 - Trisomy
 - Lymphocyte Transformation, Review, 79-6078
 - Urea, Methyl Nitroso-
 - DNA, 79-6466
 - Virus, Adeno 2
 - Immunity, Cellular, 79-6501
 - Virus-Like Particles
 - Killer Cells, 79-6502
 - Virus, Murine Leukemia
 - Precancerous Conditions, Review, 79-6083
 - Virus, Rous Sarcoma
 - Immunogenetics, 79-6498
 - Virus, SV40
 - IgG, 79-6448
 - Immunosuppression, 79-6448
- Lymphoma (General and Unspecified)**
- Acridine, 3,6-Diamino-
 - Light, 79-6287
 - Age Factors
 - Epidemiology, 79-6579
 - Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
 - Carcinogenic Metabolite, Review, 79-6017
 - Child
 - Epidemiology, Iran, 79-6589
 - Cholanthrene, 3-Methyl-
 - Histocompatibility Antigens, 79-6484
 - Neoplasm Metastasis, 79-6484

Lymphoma (General and Unspecified)
(cont'd)

- Graft vs Host Reaction
 - Morphological Study, Mouse, 79-6485
- Immunosuppression
 - Transplantation, Homologous, 79-6009
- Lactose
 - Cell Aggregation, 79-6593
- B-Lymphocytes
 - Neoplasm Circulating Cells, 79-6469
- T-Lymphocytes
 - Immunity, Cellular, 79-6468, 79-6484
- Neoplasm Metastasis
 - Mouse, 79-6541
- Neoplasms, Multiple Primary
 - Drug Therapy, 79-6009
- Neutral Red
 - Light, 79-6287
- Peptic Ulcer
 - Hemorrhage, 79-6550
- Plant Agglutinins
 - Cytochalasin B, 79-6593
 - Ricinus communis*, 79-6593
 - Vinblastine Sulfate, 79-6593
- Polish Migrants
 - England, Wales, 79-6557
- Psoralen, 8-Methoxy-
 - Ultraviolet Rays, 79-6287
- Radiation
 - Histocompatibility Antigens, 79-6484
- Sodium Azide
 - Cell Aggregation, 79-6593
- Sodium Fluoride
 - Cell Aggregation, 79-6593
- Virus, AKR Murine Leukemia
 - Crosses, Genetic, 79-6404
- Virus, Herpes Saimiri
 - DNA, Viral, 79-6425
- Virus, Moloney Murine Leukemia
 - Immunity, Cellular, 79-6486
 - Suppressor Cells, 79-6486
- Virus, Murine Leukemia
 - Genetics, 79-6405
- Virus, Rauscher Murine Leukemia
 - Immunity, Passive, 79-6486
- Lymphopenia**
 - Neutropenia
 - Virus, Feline Leukemia, 79-6419
- Lymphosarcoma**
 - Carcinoma, Epidermoid
 - Case Report, 79-6473
 - Granuloma
 - Histological Study, 79-6521
 - Leukocytes
 - Fetal Blood, 79-6429
 - T-Lymphocytes
 - Granuloma, 79-6521
 - Pancreatic Neoplasms
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
 - Thymus Neoplasms
 - Virus, Radiation Leukemia, 79-6399
 - Virus, Epstein-Barr
 - Fetal Blood, 79-6429
 - Graft vs Host Reaction, 79-6429
 - Water Pollutants
 - Chloroform Extracts, 79-6343
 - 79-6344
- Lysosomes**
 - Hepatoma
 - Cell Cycle Kinetics, 79-6229
- Macrophages**
 - Asbestos
 - Enzymes, Review, 79-6102
 - Fetal Globulins
 - Transplantation Immunology, 79-6497
 - Fibrosarcoma
 - Cholanthrene, 3-Methyl-, 79-6495
 - Growth, 79-6497
 - Radiation, Ionizing
 - Transplantation Immunology, 79-6497
 - Silicon
 - Enzymes, Review, 79-6102

Magnesium

- Cell Division
 - Fibroblasts, 79-6385
- Malaria**
 - Burkitt's Lymphoma
 - Epidemiology, Review, 79-6127

Malate Dehydrogenase

- Sebaceous Gland Neoplasms
 - Zymbal Gland, Rat, 79-6302

Maleic Acid, Diethyl Ester

- Benzo(a)pyrene
 - Lung, Binding, 79-6322
- Glutathione
 - Gastrointestinal System, 79-6219

Maltol

- see 4*H*-Pyran-4-one, 3-Hydroxy-2-methyl-

Mammary Neoplasms, Experimental

- Acridine, 3,6-Diamino-
 - Light, 79-6287
- Adenocarcinoma
 - Antibody-Dependent Cell Cytotoxicity 79-6518
 - Benz(a)anthracene, 7,12-Dimethyl-79-6299
 - Lymphocyte Depletion, 79-6517
 - 79-6518
 - Neoplasm Metastasis, 79-6517
 - Radiation, Ionizing, 79-6299, 79-6517
 - 79-6518
 - p*-Tolamide, *N*-Isopropyl- α -(2-methylhydrazino)-, 79-6299
 - Virus, Murine Mammary Tumor 79-6396
 - Water Pollutants, 79-6343, 79-6344
- Adenofibroma
 - Radiation, Ionizing, 79-6299
- Amino Acids
 - Diet, Review, 79-6041
- Benz(a)anthracene, 7,12-Dimethyl-
 - Dietary Carbohydrates, 79-6300
 - Dietary Fats, 79-6301, 79-6516
 - Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-6301
- Progesterone, 79-6345
 - Receptors, Hormone, 79-6346
- Carcinoma
 - Adenosine, Methyl Nitroso-, 79-6232
- Carcinosarcoma
 - Ultraviolet Rays, 79-6287
- Contraceptives, Oral
 - Histological Study, Dog, 79-6350
- Cyprosterone Acetate
 - Carcinogenic Potential, Dog, 79-6352
- Estrogens
 - Receptors, Hormone, 79-6346
- Histocompatibility Antigens
 - Immune Response, 79-6515
 - Transplantation Immunology, 79-6514
- Hyperplasia
 - Estradiol, 17-Ethynyl-, 79-6350
 - Megestrol Acetate, 79-6350
 - Mestranol, 79-6350
 - Neoplasm Transplantation, 79-6515
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
 - Dose-Response Study, Rat, 79-6216
- Neutral Red
 - Light, 79-6287
- Norgestrel
 - Carcinogenic Potential, Dog, 79-6352
- Phorbol
 - Strain Difference, Rat, 79-6299
- Progesterone
 - Antineoplastic Activity, 79-6345
 - Receptors, Hormone, 79-6346
- Prolactin
 - Co-carcinogenic Effect, Review 79-6027
 - Immune Response, Review, 79-6027
- Psoralen, 8-Methoxy-
 - Ultraviolet Rays, 79-6287
- Radiation, Ionizing
 - Dose-Response Study, Review

Mammary Neoplasms, Experimental
(cont'd)

- Dose-Response Study, Review 79-6070
- Neoplasm Transplantation, 79-6515
- Skin Neoplasms
 - Ultraviolet Rays, 79-6287
- Testosterone
 - Carcinogenic Potential, Dog, 79-6352
- Toxaphene
 - Carcinogenic Potential, Review 79-6003
 - Mouse, Rat, Review, 79-6003
- Urea, Methyl Nitroso-
 - Receptors, Hormone, 79-6346
- Urea, Nitroso-
 - Retinol Acetate, 79-6200
- Virus, Murine Mammary Tumor
 - Dexamethasone, 79-6395
 - DNA-DNA Hybridization, 79-6394
 - Genetics, 79-6398
 - Lactation, 79-6398

Manganese

- Feces
 - Mutagenic Activity, 79-6140
- Hydrazine
 - DNA Repair, 79-6141
- Isonicotinic Acid, 2-(2-(Benzylcarbamoyl)ethyl)hydrazide
 - DNA Repair, 79-6141
- Isonicotinic Acid Hydrazide
 - DNA Repair, 79-6141
- Isonicotinic Acid, 2-Isopropylhydrazide
 - DNA Repair, 79-6141

Medulloblastoma

- Thyroid Neoplasms
 - Radiotherapy, 79-6368

Mefloquine Hydrochloride

- Ames Test
 - Mutagenic Activity, 79-6228

Megestrol Acetate

- Mammary Neoplasms, Experimental
 - Hyperplasia, 79-6350

Melanin

- Melanoma
 - Mezerein, 79-6268
 - Phorbol 12,13-Didecanoate, 79-6268
 - 12-*O*-Tetradecanoylphorbol-13-acetate 79-6268

Melanoma

- Brain Neoplasms
 - Neoplasm Metastasis, 79-6534
- Contact Inhibition
 - Cells, Cultured, Review, 79-6091
- Eye Neoplasms
 - Histopathological Study, 79-6554
- Glycoproteins
 - Neoplasm Metastasis, 79-6534
- IgG
 - Antigen-Antibody Complex, 79-6505
- Melanin
 - Mezerein, 79-6268
 - Phorbol 12,13-Didecanoate, 79-6268
 - 12-*O*-Tetradecanoylphorbol-13-acetate 79-6268
- Membrane Proteins
 - Neoplasm Metastasis, 79-6534
- Ovarian Neoplasms
 - Neoplasm Metastasis, 79-6534
- Pigmentation
 - Epidemiology, 79-6556
- Polychlorobiphenyl Compounds
 - Carcinogenic Potential, Review 79-6112
- Skin Neoplasms
 - Strain Difference, Hamster, 79-6544
- Ultraviolet Rays
 - Epidemiology, 79-6556

Membrane Proteins

- Fibrosarcoma
 - Cholanthrene, 3-Methyl-, 79-6596
- Glycoproteins

Membrane Proteins (cont'd)

- Neoplasm Metastasis, 79-6534
- Melanoma
 - Neoplasm Metastasis, 79-6534
- Sarcoma
 - Neoplasm Metastasis, 79-6534
- Virus, Avian Sarcoma
- RNA, Messenger, 79-6380

Meningioma

- Brain Neoplasms
 - Radiation, Ionizing, 79-6529
- Radiation, Ionizing
- Case Report, 79-6529

Meningocele

- Neurofibromatosis
- Intrathoracic Defect, 79-6528

Menopause

- Ovarian Neoplasms
 - Epidemiology, Review, 79-6122
- 79-6123
- Uterine Neoplasms
 - Epidemiology, Review, 79-6124

Mercury

- Food Contamination
 - Risk Evaluation, Canada, Review
- 79-6107
- Water Pollution
 - Risk Factors, Review, 79-6109

Mesothelioma

- Asbestos
 - Adenosine Cyclic 3',5' Monophosphate, 79-6231
 - Air Pollution, 79-6105
 - Epidemiology, Review, 79-6104
 - Guanosine Cyclic 3',5' Monophosphate, 79-6231
- Multiple Myeloma
 - Asbestos, 79-6133
- Peritoneal Neoplasms
 - Asbestos, 79-6231
- Smoking
 - Epidemiology, Review, 79-6104

Mestranol

- Mammary Neoplasms, Experimental
- Hyperplasia, 79-6350

Metaplasia

- Bladder Neoplasms
 - Cell Membrane, 79-6203
- Gynecologic Neoplasms
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 79-6342
- Stomach Neoplasms
 - Precancerous Conditions, Review
- 79-6094

Methane, Azoxy-

- Colonic Neoplasms
 - Dietary Fiber, 79-6204
- Intestinal Neoplasms
 - Surgery, Operative, 79-6378

Methane, Sulfinylbis-

- Chromosome Aberrations
 - Drosophila melanogaster*, 79-6205
- 79-6209
- Sex Chromosomes, 79-6205

Methanesulfonic Acid, Ethyl Ester

- Chromosome Aberrations
 - Drosophila melanogaster*, 79-6209
- Escherichia coli*
 - Mutagenic Activity, 79-6206
- Peptides
 - Cell Transformation, Neoplastic
- 79-6599

Methanesulfonic Acid, Isopropyl Ester

- Chromosome Aberrations
 - Drosophila melanogaster*, 79-6205
- 79-6209

Methanesulfonic Acid, Methyl Ester

- Chromatids
 - Chromosome Aberrations, 79-6145

Methanesulfonic Acid, Methyl Ester

- (cont'd)
- Lymphocytes, 79-6145
- Chromosome Aberrations
 - Drosophila melanogaster*, 79-6205
- 79-6209
- Sex Chromosomes, 79-6205
- DNA
 - Antinuclear Factors, 79-6466
- T-Lymphocytes, 79-6466

Methanol

- Alanine Aminotransferase
 - Serum Levels, 79-6147
- Carbon Tetrachloride
 - Hepatotoxicity, 79-6147
- Glucosephosphatase
 - Liver, Rat, 79-6147
- Triglycerides
 - Liver, Rat, 79-6147

Methanol, (Methyl-ONN-azoxy)-, Acetate

- (Ester)
- Beta-Glucosidases
 - Ames Test, 79-6146
- Disulfide, Bis(diethylthiocarbamoyl)-
 - DNA Replication, 79-6148
- DNA Replication
 - Colon, Rat, 79-6148
- Pyrazole
 - Antineoplastic Activity, 79-6148

Methanol, (Methyl-ONN-azoxy)-

- Beta-Glucosidases
 - Ames Test, 79-6146

Methemoglobinemia

- Nitrous Acid, Sodium Salt
 - Reticuloendothelial System, Review
- 79-6061

Mezerein

- 5,8,11,14-Eicosatetraenoic Acid
 - Fibroblasts, Chick Embryo, 79-6277
- Melanoma
 - Melanin, 79-6268
- Platelet Aggregation
 - Prostaglandin Synthase, 79-6272
- Prostaglandins
 - Fibroblasts, Chick Embryo, 79-6277

Microsomes

- Ethane, 1,2-Dibromo-
 - Macromolecules, Binding, 79-6150
- Ethane, 1,2-Dichloro-
 - Macromolecules, Binding, 79-6150

Microsomes, Liver

- Acetamide, *N*-Fluoren-2-yl-
 - Mutagenic Metabolite, 79-6167
- Peptides, 79-6167
- Acetamide, *N*-(7-Hydroxyfluoren-2-yl)-
 - Aryl Hydrocarbon Hydroxylases
- 79-6167
- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Aryl Hydrocarbon Hydroxylases
- 79-6167
- Benz(a)anthracene
 - Carcinogenic Metabolite, Review
- 79-6017
- Benz(a)anthracene, 7,12-Dimethyl-
 - Dietary Fats, 79-6301
- Dihydrodiol Metabolites, 79-6289
- Phenol, (1,1-Dimethylethyl)-4-methoxy-, 79-6301
- Benz(a)anthracene-7-methanol, 12-Methyl-
 - Dihydrodiol Metabolites, 79-6289
- 1,3-Benzenediamine, 4-Methoxy-
 - Mutagenic Metabolite, 79-6167
- Benzo(a)pyrene
 - Ames Test, 79-6318
 - DNA Adducts, 79-6335
 - Enzyme Activation, 79-6318
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - Carcinogenic Metabolite, Review
- 79-6017
- Benzo(a)pyrene 4,5-Oxide

Microsomes, Liver (cont'd)

- Mutagenic Metabolite, 79-6017
- Carbamic Acid, Diisopropylthio-, *S*-(2,3-Dichloroallyl) Ester
 - Mutagenic Metabolite, 79-6056
- Carcinogen, Chemical
 - Ames Test, 79-6242
- Cholanthrene, 3-Methyl-
 - Metabolism, 79-6312
- Citrinin
 - Mutagenic Metabolite, 79-6256
- Ethylene, Chloro-
 - Ames Test, 79-6151
- Ethylene, 1,1-Dichloro-
 - Ames Test, 79-6151
- Ethylene, 1,2-Dichloro-
 - Ames Test, 79-6151
- Ethylene, Tetrachloro-
 - Ames Test, 79-6151
- Fibrosarcoma
 - Benzo(a)pyrene, 79-6318
- Fluoren-2-amine
 - Mutagenic Metabolite, 79-6167
- Mutagens
 - Metabolic Activation, Deactivation
- 79-6157
- Pararosaniline
 - Ames Test, 79-6242
- Pyrrrolidine, 1-Nitroso-
 - Mutagenic Metabolite, 79-6212
- p*-Toluidine, *N*-Isopropyl- α -(2-methyl-ONN-azoxy)-
 - Oxidative Metabolism, 79-6244
- p*-Toluidine, *N*-Isopropyl- α -(2-methylazo)-
 - Oxidative Metabolism, 79-6244
- p*-Toluidine, *N*-Isopropyl- α -(2-methylhydrazino)-
 - Benzamide, *p*-Formyl-*N*-isopropyl-, 79-6244
- Hydrazine, Methyl-, 79-6244
- Oxidative Metabolism, 79-6244
- m*-Toluidine, *N,N*-Dimethyl-4-(phenylazo)-
 - Ames Test, 79-6242

Mirex

- Adrenal Cortex
 - Carcinogenic Potential, Review
- 79-6005

Mitochondria, Liver

- Cholanthrene, 3-Methyl-
 - Oxidative Phosphorylation, 79-6311

Mitomycin C

- Arginine
 - Chromosome Aberrations, 79-6224
- Caffeine
 - Chromatids, 79-6226
 - Chromosome Aberrations, 79-6226
- Chromatids
 - Cell Division, 79-6224
- Mutation
 - Drosophila melanogaster*, 79-6365
- 12-O-Tetradecanoylphorbol-13-acetate
 - Chromatids, 79-6273

Mitosis

- Estrogens
 - Cell Transformation, Neoplastic, Review, 79-6031
- Platinum, Diamminedichloro-, *cis*-
 - Chromatids, 79-6143
- Radiation, Ionizing
 - Chromatids, 79-6362

Monocytes

- Histocompatibility Antigens
 - Immune Response, Review, 79-6084
- Leukemia, Hairy Cell
 - Antibody Specificity, 79-6480
- Phagocytosis, 79-6482

Morpholine

- Nitroso Compounds
 - Precursors, Review, 79-6057
- Nitrous Acid, Sodium Salt
 - Cell Transformation, Neoplastic

Morpholine (cont'd)
Cell Transformation, Neoplastic
79-6180
Transplacental Mutagenesis, 79-6180

Morpholine, N-Nitroso-
Adenofibroma
Carcinogenic Activity, Rat, 79-6215
Air Pollution
Occupational Hazard, 79-6182
Ames Test
Mutagenic Metabolite, 79-6165
Aryl Hydrocarbon Hydroxylases
Metabolism, Liver, 79-6165
Bile Duct Neoplasms
Cholangioma, 79-6215
Carcinoma, Epidermoid
Carcinogenic Activity, Rat, 79-6215
Chromosome Aberrations
Embryo, Hamster, 79-6180
Fibroma
Carcinogenic Activity, Rat, 79-6215
Kidney Neoplasms
Precancerous Conditions, 79-6215
Liver Neoplasms
Precancerous Conditions, 79-6215
Mutation
Azaguanine, Thioguanine Resistance
79-6180
Embryo, Hamster, 79-6180
Nitrous Acid, Sodium Salt
Stomach, Hamster, 79-6180

Mouth Neoplasms
Areca
Epidemiology, Review, 79-6099
Benz(a)anthracene, 7,12-Dimethyl-
Benzene, 1-Chloro-2,4-dinitro-
79-6298
Benzene, 1-Chloro-2,4-dinitro-
Hypersensitivity, Delayed, 79-6298
Carcinoma
Leukoplakia, Oral, 79-6531
Leukoplakia, Oral
Smoking, 79-6531
Tobacco
Epidemiology, Review, 79-6099

Multiple Myeloma
Antigens
Antibody Specificity, 79-6504
Isolation and Characterization
79-6504
Asbestosis
Case Report, 79-6133
Idiotypic Determinants
Immunocytochemical, Ultrastructural
Study, 79-6503
IgA
Asbestos, 79-6133
IgG
Asbestos, 79-6133
Mesothelioma
Asbestos, 79-6133
Myeloma Proteins
Idiotypic Determinants, 79-6503
Lymphocytes, 79-6503
Radiation, Ionizing
Epidemiology, 79-6576
Occupational Hazard, 79-6576

Muramidase
Leukemia, Hairy Cell
B-Lymphocytes, 79-6480

Muscles
12-O-Tetradecanoylphorbol-13-acetate
Cell Differentiation, 79-6271

Mutagens
Ames Test
Bioassays, Review, 79-6048
S9 Fraction, 79-6157
Shale Oil Products, 79-6130
Chromosome Aberrations
Bioassays, Review, 79-6048
Colonic Neoplasms
Feces, 79-6575
Environmental Hazard

Mutagens (cont'd)
Thresholds, Review, 79-6045, 79-6108
Feces
Ames Test, 79-6575
Chromosome Aberrations, 79-6140
Metabolism
DNA Adducts, Review, 79-6008
Microsomes, Liver
Metabolic Activation, Deactivation
79-6157

Mutation
Acridine
Genetic Effects, Review, 79-6013
Benz(a)anthracene, 7-Bromomethyl-
Azaguanine Resistance, 79-6319
Benzo(a)pyrene
Azaguanine Resistance, 79-6319
Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxo-
7,8,9,10-tetrahydro-
Azaguanine Resistance, 79-6319
Benzo(a)pyrene 4,5-Oxide
Azaguanine Resistance, 79-6319
Cycloheximide
Ribosomes, 79-6159
Cyclophosphamide
Yeasts, 79-6191
Diethylamine, 2,2'-Dichloro-N-methyl-
Yeasts, 79-6191
DNA Repair
Yeasts, 79-6191
Drosophila melanogaster
Sex Chromosomes, 79-6365
Ethidium Bromide
Saccharomyces cerevisiae, 79-6152
Ethylene Oxide
Risk Evaluation, Review, 79-6049
Mitomycin C
Drosophila melanogaster, 79-6365
Morpholine, N-Nitroso-
Azaguanine, Thioguanine Resistance
79-6180
Embryo, Hamster, 79-6180
Psoralen, 3-Carboxy-
Saccharomyces cerevisiae, 79-6152
Radiation, Ionizing
Drosophila melanogaster, 79-6365
Risk Evaluation, Review, 79-6049
79-6068
Saccharomyces cerevisiae
DNA, Mitochondrial, 79-6152
Ultraviolet Rays
Yeasts, 79-6191
Uridine, 2'-Deoxy-5-fluoro-
Drosophila melanogaster, 79-6365

Mycoplasma
Interferon
Toxicity, 79-6463

Mycotoxins
Bracken Fern
Epidemiology, Review, 79-6022
Carcinogen, Environmental
Epidemiology, Review, 79-6111
Experimental Toxicology, Review
79-6104
Digestive System Neoplasms
Fusarium, Review, 79-6098
Esophageal Neoplasms
Benzylamine, N-Methyl-N-nitroso-
79-6197
2-Butanone, 3-((3-
Methylbutyl)nitrosamino)-, 79-6197
Liver Neoplasms
Epidemiology, Review, 79-6099
Penicillium roqueforti
Ribonuclease, 79-6257
RNA Polymerase, 79-6257

Myeloma Proteins
Dextrans
Antigen-Antibody Reactions, 79-6490
Immunoglobulins, Light Chain
Idiotypic Determinants, 79-6503
Multiple Myeloma
Idiotypic Determinants, 79-6503
Lymphocytes, 79-6503

Myofibrils
12-O-Tetradecanoylphorbol-13-acetate
Cell Differentiation, 79-6271

NADPH Cytochrome C Reductase
Acetamide, N-Fluorenyl-2-yl-
Ames Test, 79-6166

2-Naphthalenecetic Acid, 6-Methoxy- α -methyl-
12-O-Tetradecanoylphorbol-13-acetate
Prostaglandins E, 79-6274

1,4-Naphthalenedione, 2-Hydroxy-
Ames Test
Mutagenic Activity, 79-6261
Toxicity
Bacterial, Eukaryotic Cells, 79-6261

Naphtho(1,8-gh:5,4-g'h')diquinoline
Sarcoma
Carcinogenic Activity, 79-6330

1-Naphthylamine
Smoke Condensate
1-Naphthylamine, 2-Methyl-, 79-6241

2-Naphthylamine
Bladder Neoplasms
Occupational Hazard, 79-6011

1-Naphthylamine, 2-Methyl-
Smoke Condensate
Aromatic Amines, 79-6241

Nasopharyngeal Neoplasms
Virus, Epstein-Barr
Cell Line, 79-6428
Transplantation, Heterologous
79-6428

Neoplasm Metastasis
Adenocarcinoma
Dipropylamine, 2-Hydroxy-N-nitroso-
2'-oxo-, 79-6196
T-Lymphocytes, 79-6517
Radiation, Ionizing, 79-6517
Amino Acids
Diet, Review, 79-6041
Antigens
Tumor Dormancy, Review, 79-6088
Bone Neoplasms
Sarcoma, Ewing's, 79-6562
Brain Neoplasms
Carcinoma, Bronchiolar, 79-6532
Melanoma, 79-6534
Breast Neoplasms
Histocytes, 79-6548
Lymph Nodes, 79-6549
Cyclophosphamide
Radiation, Ionizing, 79-6161
Fibrosarcoma
Hypothyroidism, 79-6595
Lung, 79-6493
Thyroxine, 79-6595
Transplantation, Homologous, 79-6493

Hepatosarcoma
Diethylamine, N-Nitroso-, 79-6195
Mouse, 79-6541

Leukemia
Mouse, 79-6541

Lung Neoplasms
Cyclophosphamide, 79-6161
Sarcoma, 79-6534
Virus, Herpes Simplex 2, 79-6532
Virus, Murine Sarcoma, 79-6538

Lymphoma
Cholanthrene, 3-Methyl-, 79-6484
Mouse, 79-6541

Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6517

Melanoma
Glycoproteins, 79-6534
Membrane Proteins, 79-6534

Membrane Proteins
Glycoproteins, 79-6534

Ovarian Neoplasms
Epidemiology, Review, 79-6119
Melanoma, 79-6534
Sarcoma

Neoplasm Metastasis (cont'd)

- Hypothyroidism, 79-6595
- Membrane Proteins, 79-6534
- Nickel Sulfide, 79-6142
- Thyroxine, 79-6595
- Virus, Murine Sarcoma
- Sialoglycoproteins, 79-6538

Neoplasm Recurrence, Local

- Abdominal Neoplasms
- Lymphangiosarcoma, 79-6370

Neoplasm Regression, Spontaneous

- Virus, Friend Murine Leukemia
- Strontium, 79-6408
- Thymus Gland, 79-6408

Neoplasm Transplantation

- Fibrosarcoma
- Cholanthrene, 3-Methyl-, 79-6496
- Hypersensitivity, Delayed, 79-6495
- Hepatoma
- Acetamide, N-Fluorenyl-, 79-6172
- Chlordane, 79-6172
- Mammary Neoplasms, Experimental
- Hyperplasia, 79-6515
- Radiation, Ionizing, 79-6515

Neoplasms (General and Unspecified)

- Age Factors
- Mouse, 79-6541
- Alcoholic Beverages
- Epidemiology, Review, 79-6022
- Cholesterol
- Epidemiology, Review, 79-6026
- Diet
- Epidemiology, Review, 79-6022
- 79-6104
- Dietary Fats
- Epidemiology, Review, 79-6026
- Estrogens
- Chromatin, Review, 79-6030
- Receptors, Hormone, 79-6030
- Immunosuppression
- Aging, Review, 79-6088
- Tumor Dormancy, Review, 79-6088
- Nucleic Acids
- Hypermethylation, Review, 79-6059
- Oncogenic Viruses
- Vertical Transmission, Review
- 79-6072
- Transplantation
- Immunosuppression, Review, 79-6085
- Kidney Failure, Chronic, 79-6085

Neoplasms, Embryonal and Mixed

- Skin Neoplasms
- Ultrastructural Study, 79-6535

Neoplasms, Experimental

- Ammonium, (5-Amino-5-carboxypentyl)trimethyl-
- Growth, Review, 79-6059
- Carcinogen, Chemical
- Dose-Response Study, Review
- 79-6032, 79-6058
- Hamster, Review, 79-6044
- Carcinogen, Environmental
- Risk Evaluation, Review, 79-6043
- Immunity, Passive
- Mouse, Review, 79-6086
- Nitrosamines
- Dose-Response Study, Review
- 79-6058
- Transplantation Immunology
- Mouse, Review, 79-6086
- Virus, Rous Sarcoma
- Mouse, Nude, 79-6386
- Virus, SV40
- Histocompatibility Antigens, 79-6509
- Paraformaldehyde Fixation, 79-6509

Neoplasms, Multiple Primary

- Astrocytoma
- Carotid Body Tumor, 79-6376
- Autosome Abnormalities
- Case Report, 79-6540
- Breast Neoplasms
- Epidemiology, Review, 79-6117

Neoplasms, Multiple Primary (cont'd)

- Colonic Neoplasms
- Genetics, 79-6540
- Erythroleukemia
- Drug Therapy, 79-6009
- Lymphoma
- Drug Therapy, 79-6009
- Nephroblastoma
- Abnormalities, 79-6546
- Pancreatic Neoplasms
- Dipropylamine, 2-Hydroxy-N-nitroso-2'-oxo-, 79-6196
- Pheochromocytoma
- Case Report, 79-6547
- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
- Carcinogenic Activity, Rat, 79-6211
- Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-
- Carcinogenic Activity, Rat, 79-6211
- Uterine Neoplasms
- Genetics, 79-6540

Neoplasms, Radiation-Induced

- Radiation, Ionizing
- Dose-Response Study, Review
- 79-6070

Nephritis, Interstitial

- Anthraquinone, 1-Amino-2-methyl-
- Diet, 79-6262
- Hepatoma
- Diet, 79-6262

Nephroblastoma

- Hamartoma
- Genetics, 79-6546
- Histological Study, 79-6545
- Histocompatibility Antigens
- Antigen Frequency, 79-6510
- Neoplasms, Multiple Primary
- Abnormalities, 79-6546

Nerve Tissue

- Synovioma
- Histological Study, 79-6527

Nerve Tissue Proteins

- Benzo(a)pyrene
- Astrocytes, 79-6321
- Cell Transformation, Neoplastic
- 79-6321

Nervous System Neoplasms

- Alkylating Agents
- DNA Repair, Review, 79-6065

Neuraminidase

- Virus, Murine Sarcoma
- Sialic Acid, 79-6538

Neurilemmoma

- Sarcoma
- Drug Therapy, 79-6211

Neuroblastoma

- Histocompatibility Antigens
- Antigen Frequency, 79-6510

Neurofibromatosis

- Meningocele
- Intrathoracic Defect, 79-6528

Neuroglia

- Benzo(a)pyrene
- Ultrastructural Study, 79-6320

Neurospora crassa

- Cycloheximide
- Drug Resistance, 79-6159
- Ribosomes, 79-6159

Neutral Red

- Lymphoma
- Light, 79-6287
- Mammary Neoplasms, Experimental
- Light, 79-6287
- Skin Neoplasms
- Light, 79-6287
- Thyroid Neoplasms
- Light, 79-6287

Neutrons

- Radiation, Ionizing
- Cell Transformation, Neoplastic
- 79-6360

Neutropenia

- Virus, Feline Leukemia
- Lymphopenia, 79-6419
- Precancerous Conditions, 79-6419

Nickel

- Air Pollution
- Epidemiology, Review, 79-6054
- 79-6105
- Lung Neoplasms
- Air Pollution, 79-6054
- Smoking
- Co-carcinogenic Effect, Review
- 79-6053, 79-6054

Nickel Carbonyl

- Air Pollution
- Epidemiology, Review, 79-6054

Nickel Sulfide

- Sarcoma
- Mouse, Nude, 79-6499
- Neoplasm Metastasis, 79-6142
- Transplantation Immunology, 79-6499
- X-Ray Diffraction and Autoradiographic Study, 79-6142

Nicotine

- Benzo(a)pyrene
- Lung, Binding, 79-6322

Nitric Acid

- Food Contamination
- Risk Factors, Review, 79-6110
- Gastrointestinal Neoplasms
- Epidemiology, Review, 79-6101
- Nitroso Compounds
- Water Pollution, Review, 79-6109

Nitrosamines

- Air Pollution
- Carcinogenic Potential, 79-6182
- Carcinogen, Environmental
- Epidemiology, Review, 79-6111
- Formaldehyde
- Hypermethylation, Review, 79-6059
- Neoplasms, Experimental
- Dose-Response Study, Review
- 79-6058
- Nitrous Acid
- Ascorbic Acid, 79-6245
- Nitrous Acid, Sodium Salt
- Lipids, 79-6179
- Milk, 79-6179
- Pancreatic Neoplasms
- Carcinoma, Ductal, 79-6508

Nitroso Compounds

- Environmental Hazard
- Precursors, Review, 79-6057
- Nitric Acid
- Water Pollution, Review, 79-6109
- Organ Specificity
- Carcinogenic Metabolite, Review
- 79-6064
- Pesticides
- Water Pollution, Review, 79-6109
- Staphylococcus aureus*
- Co-carcinogenic Effect, Review
- 79-6057
- Thiocyanic Acid
- Co-carcinogenic Effect, Review
- 79-6057

Nitrous Acid

- Adenosine, Methyl Nitroso-
- Carcinogenic Activity, Mouse, 79-6232
- Nucleoside Interaction, 79-6232
- Food Additives
- Carcinogenic Potential, Review
- 79-6060
- Food Contamination
- Risk Factors, Review, 79-6110
- Nitrosamines
- Ascorbic Acid, 79-6245

Nitrous Acid, Sodium Salt
 Dimethylamine, *N*-Nitroso-
 Stomach, Hamster, 79-6180
Linoleic Acid, Methyl Ester
 Reaction Products, 79-6179
Methemoglobinemia
 Reticuloendothelial System, Review
 79-6061
Morpholine
 Cell Transformation, Neoplastic
 79-6180
 Transplacental Mutagenesis, 79-6180
Morpholine, *N*-Nitroso-
 Stomach, Hamster, 79-6180
Nitrosamines
 Lipids, 79-6179
 Milk, 79-6179
Norepinephrine
 Glioma
 Adenosine Cyclic 3',5' Monophos-
 phate, 79-6164
Pheochromocytoma
 Phenethanolamine *N*-
 Methyltransferase, 79-6547
Trifluoperazine
 Receptors, Hormone, 79-6164
Norethisterone
 Endometrial Hyperplasia
 Drug Therapy, 79-6348
Norgestrel
 Mammary Neoplasms, Experimental
 Carcinogenic Potential, Dog, 79-6352
Norharman
 Benzo(a)pyrene
 Co-carcinogenic Effect, Review
 79-6016
Nose Neoplasms
 Carcinoma, Epidermoid
 Pentylamine, *N*-Methyl-*N*-nitroso-
 79-6214
Papilloma
 Pentylamine, *N*-Methyl-*N*-nitroso-
 79-6214
Nuclear Reactors
 Plutonium
 Air Pollution, 79-6374
 Particle Collection, 79-6374
Nucleic Acids
 Benzenamine, *N,N*-Dimethyl-4-((3-
 methylphenyl)azo)-
 Hepatocarcinogenesis, 79-6236
 Glioma
 Amino Acids, 79-6201
 Urea, Nitroso-, 79-6201
 Neoplasms
 Hypermethylation, Review, 79-6059
Oncogenic Viruses
 Transformation, Genetic, Review
 79-6073
 4-Stilbenamine, *N,N*-Dimethyl-
 Dose-Response Study, Binding
 79-6340
 Liver, Rat, 79-6340
Nucleoproteins
 Adenocarcinoma
 Hydrazine, 1,2-Dimethyl-, 79-6177
 Beryllium
 Binding, 79-6134
Nucleosides
 Benzo(a)pyrene
 Diol Epoxide, 79-6324
Nucleotides
 Virus, Avian Sarcoma
 Phosphotransferases, ATP, 79-6383
Obesity
 Ovarian Neoplasms
 Epidemiology, 79-6573
 Uterine Neoplasms
 Epidemiology, Finland, 79-6568

Obesity (cont'd)
 Epidemiology, Israel, 79-6567
Occupational Hazard
 Acrylonitrile
 Risk Factors, 79-6181
 Asthma
 Epidemiology, Review, 79-6115
 Bladder Neoplasms
 Benzidine, 79-6011
 Epidemiology, Review, 79-6011
 2-Naphthylamine, 79-6011
 Carbamoyl Chloride, Dimethyl-
 Carcinogenic Potential, Review
 79-6113
 Carcinogen, Chemical
 Thresholds, 79-6106
 Coal
 Epidemiology, Australia, 79-6585
 Coal Tar
 Epidemiology, Review, 79-6097
 Dimethylamine, *N*-Nitroso-
 Air Pollution, 79-6182
 Ethane, 1,1,1-Trichloro-2,2-bis(*p*-
 chlorophenyl)-
 Epidemiology, Review, 79-6047
 Ether, Bis(chloromethyl)-
 Epidemiology, Review, 79-6113
 Ethylene, Chloro-
 Epidemiology, Review, 79-6113
 Ethylene, Chloro- Polymer
 Toxicity, Review, 79-6102
 Fluorescein, Disodium Salt
 Air Pollution, 79-6263
 Leukemia, Myelocytic
 Radiation, Ionizing, 79-6576
 Lung Neoplasms
 Arsenic, 79-6115
 Asbestos, 79-6115
 Chromic Acid, 79-6115
 Coal, 79-6585
 Epidemiology, Review, 79-6053
 79-6054, 79-6115
 Gold, 79-6585
 Radiation, Ionizing, 79-6576
 Uranium, 79-6371
 Morpholine, *N*-Nitroso-
 Air Pollution, 79-6182
 Multiple Myeloma
 Radiation, Ionizing, 79-6576
 Pancreatic Neoplasms
 Radiation, Ionizing, 79-6576
 Pneumoconiosis
 Epidemiology, Review, 79-6115
 Respiratory Tract Neoplasms
 Asbestos, 79-6570
 Silicosis
 Gold, 79-6585
 Thresholds
 Risk Evaluation, Review, 79-6106
Oligodendroglioma
 Brain Neoplasms
 Urea, Nitroso-, 79-6201
 Spinal Cord Neoplasms
 Urea, Ethyl Nitroso-, 79-6210
 Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Drug Therapy, 79-6211
Oligosaccharides
 Plasmacytoma
 Binding Sites, Antibody, 79-6490
Oncogenic Viruses
 Bacteria
 Virus Activation, 79-6463
 Carcinogen, Chemical
 Virus Activation, Review, 79-6073
 Fetal Globulins
 Immune Response, Review, 79-6039
 Neoplasms
 Vertical Transmission, Review
 79-6072
 Nucleic Acids
 Transformation, Genetic, Review
 79-6073
 Transplantation Immunology
 Fetal Globulins, Review, 79-6081

Oncogenic Viruses (cont'd)
 Virus Activation
 Hamster, Review, 79-6079
 Virus-Like Particles
 Hamster, Review, 79-6079
Opium
 Bladder Neoplasms
 Epidemiology, Iran, 79-6581
 Esophageal Neoplasms
 Epidemiology, 79-6565
Ornithine Carbamoyltransferase
 Benzenamine, *N,N*-Dimethyl-4-((3-
 methylphenyl)azo)-
 Liver, Rat, 79-6236
Ornithine Decarboxylase
 Benzenamine, *N,N*-Dimethyl-4-((3-
 methylphenyl)azo)-
 Liver, Rat, 79-6236
 Chalcones
 Precancerous Conditions, 79-6275
 Dibutyl Cyclic AMP
 Precancerous Conditions, 79-6275
 Phorbol 12,13-Dibenzate
 Cell Division, 79-6275
 12-*O*-Tetradecanoylphorbol-13-acetate
 Cell Division, 79-6275
 Tumor Promoting Activity, 79-6275
Osteitis Deformans
 Giant Cell Tumors
 Case Report, 79-6533
 Sarcoma
 Epidemiology, 79-6588
 Skull Neoplasms
 Sarcoma, 79-6588
Ovarian Neoplasms
 Adenocarcinoma
 Water Pollutants, 79-6343
 Asbestos
 Occupational Hazard, Review, 79-6123
 Burkitt's Lymphoma
 Nonendemic Disease, 79-6524
 Contraceptives, Oral
 Risk Factors, 79-6573
 Cystadenocarcinoma
 Epidemiology, Dog, 79-6121
 Cystadenoma
 Epidemiology, Dog, 79-6121
 Diagnosis and Prognosis
 Histological Study, Review, 79-6119
 Environmental Hazard
 Epidemiology, Review, 79-6123
 Estrogens
 Epidemiology, Review, 79-6120
 Gallbladder Diseases
 Epidemiology, 79-6573
 Hysterectomy
 Epidemiology, Review, 79-6120
 Marital Status
 Epidemiology, 79-6587
 Melanoma
 Neoplasm Metastasis, 79-6534
 Menopause
 Epidemiology, Review, 79-6122
 79-6123
 Neoplasm Metastasis
 Epidemiology, Review, 79-6119
 Neuroendocrinology
 Entropy, Review, 79-6096
Obesity
 Epidemiology, 79-6573
 Parity
 Epidemiology, 79-6587
 Epidemiology, Review, 79-6122
 Polyps
 Epidemiology, 79-6573
 Talc
 Occupational Hazard, Review, 79-6123
 Theca Cell Tumor
 Epidemiology, Dog, 79-6121
Oxazole, 2,5-Diphenyl-
 B-Lymphocytes
 Enzyme Inhibition, 79-6313

Oxidoreductases

- Benzo(a)pyrene
 - Mutagenic Metabolite, 79-6329
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxo-7,8,9,10-tetrahydro-Metabolism, 79-6329
- Ear Neoplasms
 - Zymbal Gland, Rat, 79-6302
- Sebaceous Gland Neoplasms
 - Benzo(a)anthracene, 7,12-Dimethyl-79-6302
- trans*-Stilbene Oxide
 - Liver, Rat, 79-6316

Oxirane, 1-Pyrenyl-

- Mutagenic Activity
 - Hamster V70 Cells, 79-6336

Paget's Disease of Bone
see Osteitis Deformans**Pancreatic Neoplasms**

- Adenocarcinoma
 - Dipropylamine, 2-Hydroxy-*N*-nitroso-2'-oxo-, 79-6196
- Adenoma
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Animal Model, Nude Mouse
 - Carcinoma, Ductal, 79-6508
- Carcinoma
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
 - 79-6154
 - Serine, Diazoacetate (Ester), 79-6508
 - Transplantation, Heterologous
 - 79-6508
- Carcinoma, Ductal
 - Nitrosamines, 79-6508
 - Transplantation, Heterologous
 - 79-6508
- Islet Cell Tumor
 - Strain Difference, Hamster, 79-6544
- Lymphosarcoma
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Neoplasms, Multiple Primary
 - Dipropylamine, 2-Hydroxy-*N*-nitroso-2'-oxo-, 79-6196
- Radiation, Ionizing
 - Epidemiology, 79-6576
 - Occupational Hazard, 79-6576
- Smoke Condensate
 - Transplacental, Neonatal Carcinogenesis, 79-6285
- Smoking
 - Epidemiology, Review, 79-6126

Papilloma

- Esophageal Neoplasms
 - Benzylamine, *N*-Methyl-*N*-nitroso-79-6233
- Nose Neoplasms
 - Pentylamine, *N*-Methyl-*N*-nitroso-79-6214
- Skin Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-79-6295
 - Chrysene, 1,2-Dihydro-, 79-6304
- Stomach Neoplasms
 - Aniline, *N,N*-Methyl-*p*-(phenylazo)-, Hydroxy-, 79-6246

Paraffin Oil

- Solvents
 - Chromosome Aberrations, 79-6238

Paraproteinemas

- Aging
 - T-Lymphocytes, 79-6467
- B-Lymphocytes
 - Lymphocyte Cooperation, 79-6467

Pararosaniline

- Microsomes, Liver
 - Ames Test, 79-6242

Parathyroid Neoplasms

- Adenomatosis, Familial Endocrine

Parathyroid Neoplasms (cont'd)
Genetics, Review, 79-6093**Parity**

- Ovarian Neoplasms
 - Epidemiology, 79-6587

Parotid Neoplasms

- Sarcoma
 - Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153

Patulin

- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 - Ribonuclease, 79-6257
- Ribonuclease
 - Enzyme Inhibition, 79-6257
- RNA Polymerase
 - RNA Replication, 79-6257

Pectin

- Adenocarcinoma
 - Hydrazine, 1,2-Dimethyl-, 79-6176
- Ear Neoplasms
 - Adenocarcinoma, 79-6176
- Intestinal Neoplasms
 - Glucuronidase, 79-6176

Penicillium roqueforti

- Mycotoxins
 - Ribonuclease, 79-6257
 - RNA Polymerase, 79-6257

D-erythro-Pentose, 2-Deoxy-

- Cholanthrene, 3-Methyl-
 - Oxidative Phosphorylation, 79-6311

Pentoses

- Intestinal Neoplasms
 - Dietary Fiber, 79-6559

Pentylamine, *N*-Methyl-*N*-nitroso-

- Esophageal Neoplasms
 - Carcinoma, Epidermoid, 79-6214
- Dose-Response Study, Rat, 79-6214
- Nose Neoplasms
 - Carcinoma, Epidermoid, 79-6214
- Papilloma, 79-6214

Peptic Ulcer

- Hemorrhage
 - Salicylic Acid, 79-6550
- Leukemia
 - Hemorrhage, 79-6550
- Lymphoma
 - Hemorrhage, 79-6550

Peptide Hydrolases

- Virus, Adeno 2
 - Arginine, 79-6457
 - Isolation and Characterization
 - 79-6455
 - Temperature Sensitive Mutants
 - 79-6455

Peptides

- Acetamide, *N*-Fluorenyl-
 - Microsomes, Liver, 79-6167
- Cell Transformation, Neoplastic
 - Butyric Acid, 79-6599
- Hepatoma
 - Australia Antigen, 79-6462
- Methanesulfonic Acid, Ethyl Ester
 - Cell Transformation, Neoplastic
 - 79-6599
- Virus Adeno 2
 - Amino Acids, 79-6454
 - Cell Transformation, Neoplastic
 - 79-6454
 - RNA, Messenger, 79-6454
 - RNA, Viral, 79-6456
- Virus, Epstein-Barr
 - Immunoprecipitation, 79-6431
- Virus, Herpes Simplex 1
 - Cell Transformation, Neoplastic
 - 79-6599
- Virus, Polyoma
 - Cell Transformation, Neoplastic
 - 79-6599

Peritoneal Neoplasms

- Mesothelioma
 - Asbestos, 79-6231

Peroxidases

- Hepatoma
 - Endocytosis, 79-6229

Perylene

- Ames Test
 - Soot Extract, 79-6326

Pesticides

- Nitroso Compounds
 - Water Pollution, Review, 79-6109

Petroleum

- Ames Test
 - Shale Oil Products, 79-6130

Phagocytosis

- Leukemia, Hairy Cell
 - Acid Phosphatase, 79-6525

Phenanthrene

- Diol Epoxides
 - Mutagenic Activity, 79-6304

Phenanthrene, 1,2-Dihydroxy-3,4-epoxy-

- 1,2,3,4-tetrahydro-
 - Ames Test
 - Mutagenic Activity, 79-6304

Phenanthrene, 3,4-Epoxy-1,2,3,4-

- tetrahydro-
 - Skin Neoplasms
 - Diol Epoxides, 79-6304

Phenethanolamine *N*-Methyltransferase

- Pheochromocytoma
 - Norepinephrine, 79-6547

Phenol, (1,1-Dimethylethyl)-4-methoxy-

- Benz(a)anthracene, 7,12-Dimethyl-
 - Ames Test, 79-6301
 - DNA, Binding, 79-6291
 - Microsomes, Liver, 79-6301
- Lung Neoplasms
 - Lactic Acid, 79-6187
- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-79-6301

Phenol, 2,4,5-Trichloro-

- Environmental Hazard
 - Quantitation Method, Review, 79-6012

Phenylalanine, 4-Fluoro-

- Virus, SV40
 - Antigens, Neoplasm, 79-6446
 - DNA Replication, 79-6446

***m*-Phenylenediamine**

- Mutagenic Activity
 - Germ Cells, Rat, 79-6213

***o*-Phenylenediamine, 4-Nitro-**

- Mutagenic Activity
 - Germ Cells, Rat, 79-6213

***p*-Phenylenediamine, 2-Nitro-**

- Mutagenic Activity
 - Germ Cells, Rat, 79-6213

***p*-Phenylenediamine**

- Liver
 - Binding, 79-6237

Pheochromocytoma

- Neoplasms, Multiple Primary
 - Case Report, 79-6547
- Norepinephrine
 - Phenethanolamine *N*-Methyltransferase, 79-6547
- Pyrocatechol, 4-(2-Aminoethyl)-
 - Blood Pressure, 79-6547
 - Dopamine Beta-Hydroxylase, 79-6547

Phorbol

- Benz(a)anthracene, 7,12-Dimethyl-
 - Co-carcinogenic Effect, 79-6299
- Leukemia, Lymphocytic
 - Benz(a)anthracene, 7,12-Dimethyl-

Phorbol (cont'd)
Benz(a)anthracene, 7,12-Dimethyl-
79-6299
Carcinogenic Activity, Mouse, 79-6189
Dimethylamine, *N*-Nitroso-, 79-6189
Liver Neoplasms
Adenoma, 79-6189
Dimethylamine, *N*-Nitroso-, 79-6189
Transplacental Carcinogenesis
79-6266
Tritium, 79-6266
Lung Neoplasms
Adenoma, 79-6266
Transplacental Carcinogenesis
79-6266
Tritium, 79-6266
Mammary Neoplasms, Experimental
Strain Difference, Rat, 79-6299
Prostaglandins E
Epidermis, Mouse, 79-6274

Phorbol, 12-Deoxy-
Liver Neoplasms
Adenoma, 79-6189

Phorbol 12,13-Diacetate
Prostaglandins E
Epidermis, Mouse, 79-6274

Phorbol 12,13-Dibenzoate
5,8,11,14-Eicosatetraenoic Acid
Fibroblasts, Chick Embryo, 79-6277
Ornithine Decarboxylase
Cell Division, 79-6275
Prostaglandins
Fibroblasts, Chick Embryo, 79-6277
Prostaglandins E
Epidermis, Mouse, 79-6274
Putrescine
Epidermis, Mouse, 79-6275

Phorbol 12,13-Didecanoate
5,8,11,14-Eicosatetraenoic Acid
Fibroblasts, Chick Embryo, 79-6277
Melanoma
Melanin, 79-6268
Platelet Aggregation
Prostaglandin Synthase, 79-6272
Prostaglandins
Fibroblasts, Chick Embryo, 79-6277
Prostaglandins E
Epidermis, Mouse, 79-6274

Phorbol Esters
Glycoproteins
Cell Membrane, 79-6267
Fibroblasts, 79-6267
Liver Neoplasms
Dimethylamine, *N*-Nitroso-, 79-6189

Phosgene
Carbon Tetrachloride
Liver, Rat, 79-6149
Metabolism
Liver, Rat, 79-6149

Phosphatidylcholines
Benz(a)anthracene, 7,12-Dimethyl-
Biological Membranes, 79-6317
Benzo(a)pyrene
Biological Membranes, 79-6317

Phosphoglycerate Kinase
Cholanthrene, 3-Methyl-
Phenotype, 79-6306
Fibrosarcoma
Cholanthrene, 3-Methyl-, 79-6306

Phosphoproteins
Beryllium
Binding, 79-6134
Virus, Avian Sarcoma
Immunoprecipitation, 79-6382
Protein Kinase, 79-6382
Virus, Harvey Murine Sarcoma
Cell Transformation, Neoplastic
79-6411
Immunoprecipitation, 79-6411
Virus, Kirsten Murine Sarcoma
Cell Transformation, Neoplastic

Phosphoproteins (cont'd)
Cell Transformation, Neoplastic
79-6411
Immunoprecipitation, 79-6411

Phosphorothioic Acid, *O,O*-Dimethyl-*O*
-(2,4,5-trichlorophenyl)-
Environmental Hazard
Quantitation Method, Review, 79-6012

Phosphotransferases, ATP
Lung Neoplasms
Carbamic Acid, Ethyl Ester, 79-6187
Dimethylamine, *N*-Nitroso-, 79-6187
Virus, Avian Sarcoma
Antigen-Antibody Complex, 79-6383
Nucleotides, 79-6383

Phthalazine, 1-Hydrazino-
Ames Test
Acetone Condensation Product
79-6254
Mutagenic Activity, 79-6254

Phthalic Acid, Bis(2-butoxyethyl) Ester
Cell Division
Toxicity, Review, 79-6006

Phthalic Acid, Bis(2-ethylhexyl) Ester
Cell Division
Toxicity, Review, 79-6006
Liver
Toxicity, Review, 79-6006
Mutagenic Activity
Mice, Review, 79-6006

Phthalic Acid, Bis(methoxyethyl) Ester
Mutagenic Activity
Mice, Review, 79-6006

Pigmentation
Melanoma
Epidemiology, 79-6556

Piper nigrum
Liver Neoplasms
Carcinogenic Potential, 79-6258
Lung Neoplasms
Carcinogenic Potential, 79-6258
Skin Neoplasms
Carcinogenic Potential, 79-6258

Piperazine, 1-Methyl-4-nitroso-
Ames Test
Mutagenic Metabolite, 79-6165
Aryl Hydrocarbon Hydroxylases
Metabolism, Liver, 79-6165

Pituitary Neoplasms
Adenoma
Imidazole-1-ethanol, 2-Methyl-5-nitro-
79-6216

Plant Agglutinins
Aryl Hydrocarbon Hydroxylases
B-Lymphocytes, 79-6296
Dibenz(a,h)anthracene
Aryl Hydrocarbon Hydroxylases
79-6296
Esophageal Neoplasms
T-Lymphocytes, 79-6511
Lymphocyte Transformation
Lymphocyte Transformation, 79-6465
Lymphoma
Cytochalasin B, 79-6593
Ricinus communis, 79-6593
Vinblastine Sulfate, 79-6593
Virus, SV40
Lymphocyte Transformation, 79-6448

Plant Tumors
Agrobacterium tumefaciens
Bacteriocins, 79-6230
Plasmids, Review, 79-6037

Plasmacytoma
Dextrans
Binding Sites, Antibody, 79-6490
Endonucleases
Nucleic Acid Heteroduplexes, 79-6491
Nucleic Acid Hybridization, 79-6491

Plasmacytoma (cont'd)
IgA
Anti-Antibodies, 79-6489
IgG
Amyloid, 79-6492
Immunoglobulins, Light Chain
Chromosomes, 79-6491
DNA, 79-6491
T-Lymphocytes
Cell Differentiation, 79-6489
Receptors, Fc, 79-6489
Oligosaccharides
Binding Sites, Antibody, 79-6490

Platelet Aggregation
5,8,11-14-Eicosatetraenoic Acid
Indole-3-acetic Acid, 1-(*p*-
Chlorobenzoyl)-5-methoxy-2-
methyl-, 79-6272
Thromboxanes, 79-6272
Mezerein
Prostaglandin Synthase, 79-6272
Phorbol 12,13-Didecanoate
Prostaglandin Synthase, 79-6272
12-O-Tetradecanoylphorbol-13-acetate
Prostaglandin Synthase, 79-6272
Vasoactive Material, 79-6272

Platinum, Diamminedichloro-, *cis*-
Chromatids
Lymphocytes, 79-6143
Mitosis, 79-6143
Chromosome Aberrations
Dose-Response Study, 79-6143

Plutonium
Alpha Particles
Collagen, 79-6372
Lung, Hamster, 79-6372
Body Burden
Inhalation Study, Dog, 79-6373
Lung
Half-Life, 79-6373
Nuclear Reactors
Air Pollution, 79-6374
Particle Collection, 79-6374

Pneumoconiosis
Occupational Hazard
Epidemiology, Review, 79-6115

Poly A-U
Benz(a)anthracene, 7,12-Dimethyl-
Immune Response, Mouse, 79-6295
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6295

Poly T
Virus, SV40
Antigens, Neoplasm, 79-6441

Poly U
Acridine, 9-Amino-
DNA, Binding, 79-6265
Acridine, 3,6-Bis(dimethylamino)-
DNA, Binding, 79-6265
Acridine, 3,6-Diamino-
DNA, Binding, 79-6265
Fibroblasts
DNA, Binding, 79-6265

Polyamines
**Benzenamine, *N,N*-Dimethyl-4-((3-
methylphenyl)azo)-**
Hepatocarcinogenesis, 79-6236

Polychlorobiphenyl Compounds
Aryl Hydrocarbon Hydroxylases
Cells, Cultured, 79-6249
Diethylamine, *N*-Nitroso-
Metabolism, Review, 79-6112
Gastritis
Carcinogenic Potential, Review
79-6112
Hyperplasia
Dermatologic Effects, Review, 79-6112
Liver Neoplasms
Carcinogenic Potential, Review
79-6112

Polychlorobiphenyl Compounds (cont'd)

- Melanoma
 - Carcinogenic Potential, Review 79-6112
- Water Pollution
 - Risk Factors, Review, 79-6109

Polycyclic Hydrocarbons

- Carcinogen, Environmental
 - Epidemiology, Review, 79-6111
- Cell Division
 - Gene Deletion, Review, 79-6019
- Charge Distribution
 - Carbonium Ion, 79-6283
 - Carcinogenic Potential, 79-6283
 - Diol Epoxides, 79-6283
- Electron Energy
 - Carcinogenic Metabolite, 79-6282
 - Molecular Orbital Calculations 79-6282
- Formaldehyde
 - Hypermethylation, Review, 79-6059
- Retinol
 - Metabolism, Review, 79-6019
- Smoking
 - Co-carcinogenic Effect, Review 79-6113
- Steroids
 - Chromosomes, Review, 79-6019
- Water Pollution
 - Risk Factors, Review, 79-6109

Polylysine

- Benz(a)anthracene, 7,12-Dimethyl-Biological Membranes, 79-6317
- Benzo(a)pyrene
 - Biological Membranes, 79-6317

Polyps

- Gastrointestinal Neoplasms
 - Genetics, Review, 79-6100
- Gynecologic Neoplasms
 - Hemorrhage, 79-6551
- Intestinal Neoplasms
 - Adenocarcinoma, 79-6175
- Ovarian Neoplasms
 - Epidemiology, 79-6573
- Stomach Neoplasms
 - Precancerous Conditions, Review 79-6094

Polyribosomes

- Dimethylamine, *N*-Nitroso-RNA, Transfer Methyltransferases 79-6185
- Virus, Adeno 2
 - RNA, Messenger, 79-6453
- Virus, Avian Sarcoma
 - RNA, Messenger, 79-6380

Porphyria

- Ultraviolet Rays
 - DNA Repair, 79-6354
 - DNA Replication, 79-6354

Precancerous Conditions

- Adenocarcinoma
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-79-6221
- Aflatoxin B1
 - Lactate Dehydrogenase, 79-6280
- Bladder Neoplasms
 - Urea, Methyl Nitroso-, 79-6203
- Chalones
 - Ornithine Decarboxylase, 79-6275
- Dibutyl Cyclic AMP
 - Ornithine Decarboxylase, 79-6275
- Diethylamine, *N*-Nitroso-DNA Polymerase, 79-6190
- Esophageal Neoplasms
 - Epidemiology, Iran, 79-6563
- Hepatomas
 - Alpha Fetoproteins, 79-6234
 - Toluene-2,4-diamine, 79-6240
- Intestinal Neoplasms
 - Carcinoma In Situ, 79-6175
 - Colitis, Ulcerative, 79-6558
 - Histological Study, 79-6175
 - Hydrazine, 1,2-Dimethyl-, 79-6175

Precancerous Conditions (cont'd)

- Kidney Neoplasms
 - Morpholine, *N*-Nitroso-, 79-6215
- Liver Neoplasms
 - Acetamide, *N,N'*-Fluorene-2,7-diylbis-, 79-6171
 - Aflatoxin B1, 79-6280
 - Diethylamine, *N*-Nitroso-, 79-6194
 - Glutamyl Transpeptidase, 79-6194
 - Morpholine, *N*-Nitroso-, 79-6215
- Lung Neoplasms
 - Lactic Acid, 79-6187
- Neutropenia
 - Virus, Feline Leukemia, 79-6419
- Prostatic Neoplasms
 - Adenocarcinoma, 79-6553
- Stomach Neoplasms
 - Carcinoembryonic Antigen, 79-6512
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-79-6222
 - Virus, Feline Leukemia
 - Antigenic Determinants, 79-6419
 - Virus Replication, 79-6419
 - Virus, Murine Mammary Tumor
 - Antigens, Viral, 79-6396
 - Vulvar Neoplasms
 - Epidemiology, Review, 79-6125

Pregnancy

- Graft vs Host Reaction
- Immunogenetics, 79-6485

Procarbazine

- see *p*-Toluidine, *N*-Isopropyl- α -(2-methylhydrazino)-

Progestational Hormones

- Prolactin
 - Pharmacokinetics, 79-6352
- Somatotropin
 - Pharmacokinetics, 79-6352
- Uterine Neoplasms
 - Adenocarcinoma, 79-6028
 - Menopause, 79-6348

Progesterone

- Breast Neoplasms
 - Receptors, Hormone, 79-6347
 - 79-6349
- Mammary Neoplasms, Experimental
 - Antineoplastic Activity, 79-6345
 - Benz(a)anthracene, 7,12-Dimethyl-79-6345
 - Receptors, Hormone, 79-6346

Progesterone, 17 α -Hydroxy-

- Uterine Neoplasms
 - Pharmacokinetics, 79-6352

Prolactin

- Breast Neoplasms
 - Dietary Fats, Review, 79-6029
- Mammary Neoplasms, Experimental
 - Co-carcinogenic Effect, Review 79-6027
 - Immune Response, Review, 79-6027
- Progestational Hormones
 - Pharmacokinetics, 79-6352
- Uterine Neoplasms
 - Dietary Fats, Review, 79-6029

Propene, 1,2-Epoxy-3,3,3-trichloro-

- Ames Test
 - S9 Fraction, 79-6157
- Benzene, (Epoxyethyl)-
 - Mutagenic Activity, 79-6248
- Benzo(a)pyrene
 - Metabolism, 79-6322

1-Propanol, 2,3-Dibromo-, Phosphate

- Ames Test
 - Mutagenic Activity, Review, 79-6046

1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate

- Dibenz(a,h)anthracene
 - Aryl Hydrocarbon Hydroxylases 79-6313

Propionic Acid, 2-(*p*-Chlorophenoxy)-2-

- methyl-, Ethyl Ester
- Breast Neoplasms
 - Epidemiology, 79-6155
- Drug Therapy
 - Epidemiology, 79-6155
- Hepatomas
 - Carcinogenic Activity, Rat, 79-6154
 - Sarcoma, 79-6153
- Intestinal Neoplasms
 - Leiomyoma, 79-6154
- Liver Neoplasms
 - Histochemical Study, Peroxisomes, 79-6171
- Lung Neoplasms
 - Sarcoma, 79-6153
- Pancreatic Neoplasms
 - Adenoma, 79-6153
 - Carcinoma, 79-6153, 79-6154
 - Lymphosarcoma, 79-6153
- Parotid Neoplasms
 - Sarcoma, 79-6153
- Skin Neoplasms
 - Fibrosarcoma, 79-6154
- Stomach Neoplasms
 - Adenocarcinoma, 79-6153
- Urogenital Neoplasms
 - Adenocarcinoma, 79-6153
 - Carcinoma, Papillary, 79-6153

Prostaglandin Synthase

- Mezerein
 - Platelet Aggregation, 79-6272
- Phorbol 12,13-Didecanoate
 - Platelet Aggregation, 79-6272
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Platelet Aggregation, 79-6272

Prostaglandins

- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Indole-1-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-, 79-6277
 - Retinoic Acid, 79-6277

Prostaglandins E

- Erythroleukemia
 - 12-*O*-Tetradecanoylphorbol-13-acetate 79-6278
- Phorbol
 - Epidermis, Mouse, 79-6274
- Phorbol 12,13-Diacetate
 - Epidermis, Mouse, 79-6274
- Phorbol 12,13-Dibenzoate
 - Epidermis, Mouse, 79-6274
- Phorbol 12,13-Didecanoate
 - Epidermis, Mouse, 79-6274
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Anthranilic Acid, *N*-(α,α,α -Trifluoro-*m*-tolyl)-, 79-6274
 - Epidermis, Mouse, 79-6274
 - Fibroblasts, Chick Embryo, 79-6277
 - Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-, 79-6274
 - 2-Naphthaleneacetic Acid, 6-Methoxy- α -methyl-, 79-6274

Prostaglandins F

- Erythroleukemia
 - 12-*O*-Tetradecanoylphorbol-13-acetate 79-6278
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Epidermis, Mouse, 79-6274
 - Fibroblasts, Chick Embryo, 79-6277

Prostatic Neoplasms

- Adenocarcinoma
 - Androst-4-ene-3,17-dione, 79-6351
 - Precancerous Conditions, 79-6553
 - Testosterone, 79-6351
- Alcoholic Beverages
 - Epidemiology, 79-6564
- Androgens
 - Parabiosis, 79-6351
- Carcinoma, Epidermoid
 - 1,2,4-Benzenetriol, 5-(2-Aminoethyl)-79-6307
 - Cholanthrene, 3-Methyl-, 79-6307
 - Testosterone, 79-6307

Prostatic Neoplasms (cont'd)

- Cholanthrene, 3-Methyl-
Catecholamines, 79-6307
- Indole-3-acetic Acid, 5-Hydroxy-
79-6307
- Serotonin, 79-6307
- Hyperplasia
Histopathological Diagnosis, 79-6553
- Polish Migrants
England, Wales, 79-6557

Protein Kinase

- Virus, Avian Sarcoma
Phosphoproteins, 79-6382
- Viral Proteins, 79-6382
- Virus, Murine Sarcoma
Acting, Binding, 79-6400
- Antigen-Antibody Complex, 79-6400
- Temperature Sensitive Mutant
79-6400

Proteins

- Diethylamine, *N*-Nitroso-
Amino Acid Incorporation, 79-6192
- Liver, Rat, 79-6192
- Dimethylamine, *N*-Nitroso-
Amino Acid Incorporation, 79-6192
- Liver, Rat, 79-6192
- Peptide Chain Initiation, 79-6185
- 4-Stilbenamine, *N,N*-Dimethyl-
Dose-Response Study, Binding
79-6340
- Liver, Rat, 79-6340

Psoralen, 3-Carboxy-

- Saccharomyces cerevisiae*
Mutation, 79-6152

Psoralen, 8-Methoxy-

- Adenocarcinoma
Ultraviolet Rays, 79-6287
- Carcinoma
Light, 79-6287
- Chromatids
Lymphocytes, 79-6359
- Lymphoma
Ultraviolet Rays, 79-6287
- Mammary Neoplasms, Experimental
Ultraviolet Rays, 79-6287
- Skin Neoplasms
Photochemotherapy, Review, 79-6071
- Ultraviolet Rays
Chromatids, 79-6359
- Co-carcinogenic Effect, Review
79-6071

Purine, 2-Amino-6-methoxy-

- Acetamide, *N*-Fluorenyl-
DNA Repair, 79-6170
- Liver, Rat, 79-6170
- Dimethylamine, *N*-Nitroso-
DNA Adducts, 79-6315
- DNA, Alkylation, 79-6186
- DNA Repair, 79-6170
- Liver, Rat, 79-6170
- Urea, Methyl Nitroso-
DNA Repair, Review, 79-6065

Puromycin

- 12-*O*-Tetradecanoylphorbol-13-acetate
5,8,11,14-Eicosatetraenoic Acid
79-6277

Putrescine

- Phorbol 12,13-Dibenzoate
Epidermis, Mouse, 79-6275
- 12-*O*-Tetradecanoylphorbol-13-acetate
Epidermis, Mouse, 79-6275

Pyelonephritis

- Dimethylamine, *N*-Nitroso-
Dose-Response Study, Rat, 79-6188

Pyran Copolymer

- Leukemia L1210
Drug Therapy, 79-6478
- Vaccine Potentiation, 79-6478

4H-Pyran-4-one, 5-Hydroxy-

- 2-(hydroxymethyl)-
Ames Test
Mutagenic Activity, 79-6160

4H-Pyran-4-one, 3-Hydroxy-2-methyl-, 2-

- Ethyl Ester
Ames Test
Mutagenic Activity, 79-6160

4H-Pyran-4-one, 3-Hydroxy-2-methyl-

- Ames Test
Mutagenic Activity, 79-6160

Pyrazole

- Acetic Acid, Methylnitrosaminomethyl
Ester
Toxicity, Rat, 79-6148
- Methanol, (Methyl-*ONN*-azoxy)-, Ace-
tate (Ester)
Antineoplastic Activity, 79-6148
- Urea, Methyl Nitroso-
Toxicity, Rat, 79-6148

Pyrethrum

- Liver Neoplasms
Carcinogenic Potential, Review
79-6047

Pyridoxol

- Esophageal Neoplasms
Diet, 79-6565

Pyrocatechol, 4-(2-Aminoethyl)-

- Pheochromocytoma
Blood Pressure, 79-6547
- Dopamine Beta-Hydroxylase, 79-6547

Pyrrrolidine, 1-Nitroso-

- Escherichia coli*
Mutagenic Activity, 79-6212
- Esophagus
DNA Adducts, 79-6315
- Microsomes, Liver
Mutagenic Metabolite, 79-6212

Quinacrine

- Chromatids
Chromosome Aberrations, 79-6145
- Lymphocytes, 79-6145

Quinacrine Mustard

- Chromatids
Chromosome Aberrations, 79-6145
- Lymphocytes, 79-6145

Quinoline, 7-Chloro-4-((4-(diethylamino)-1-

- methylbutylamino)-
Ames Test
Mutagenic Activity, 79-6228
- Hepatoma
Endocytosis, 79-6229

Quinoline, 4-Nitro-, 1-Oxide

- Arginine
Chromosome Aberrations, 79-6224
- Caffeine
DNA Repair, 79-6358
- Chromatids
Cell Division, 79-6224
- DNA Repair
Lymphocytes, 79-6358
- Virus, LPV
DNA Repair, 79-6227
- Virus, RNA Tumor
DNA Repair, 79-6227

8-Quinololinol

- Vaginal Preparations
Carcinogenic Potential, Review
79-6055

Radiation

- Lymphoma
Histocompatibility Antigens, 79-6484
- Tritium
Chromatids, 79-6353

Radiation, Ionizing

- Abdominal Neoplasms
Lymphangioma, 79-6370
- Adenocarcinoma

Radiation, Ionizing (cont'd)

- Hypersensitivity, 79-6518
- Neoplasm Metastasis, 79-6517
- Antipain
Cell Transformation, Neoplastic
79-6361
- Aryl Hydrocarbon Hydroxylases
Hepatocytes, Hamster, 79-6288
- Brain Neoplasms
Meningioma, 79-6529
- Carcinogen, Environmental
Epidemiology, Review, 79-6111
- Cell Transformation, Neoplastic
Dose Fractionation, 79-6360
- Cerebellar Neoplasms
Astrocytoma, 79-6376
- Chromatids
Chromosome Aberrations, 79-6361
- DNA Replication, 79-6362
- Mitosis, 79-6362
- Chromosome Aberrations
Mouse, 79-6367
- Risk Evaluation, Review, 79-6035
- 79-6068
- Cyclophosphamide
Neoplasm Metastasis, 79-6161
- DNA
Hydroxylapatite Elution Assay
79-6591
- DNA Repair
Cell Transformation, Neoplastic
79-6361
- Mutation, Review, 79-6067
- Xeroderma Pigmentosum, 79-6067
- Drosophila melanogaster*
Mutagenic Activity, 79-6198
- Sex Chromosomes, 79-6198
- Fibrosarcoma
Benz(a)anthracene, 7,12-Dimethyl-
79-6363
- Growth, 79-6363
- Transplantation, Homologous, 79-6493
- Transplantation Immunology, 79-6363
- Food Contamination
Sex Chromosomes, 79-6364
- Leukemia
DNA, 79-6591
- In Utero Exposure, Review, 79-6069
- Leukemia, Lymphocytic
Mouse, NBZ, 79-6366
- Virus, Murine Leukemia, 79-6366
- Leukemia, Myelocytic
Chromosome Aberrations, 79-6367
- Occupational Hazard, 79-6576
- Leukemia, Radiation-Induced
T-Lymphocytes, 79-6483
- Lung Neoplasms
Occupational Hazard, 79-6576
- T-Lymphocytes
Lymphocyte Transformation, Review
79-6078
- Macrophage Activation, 79-6468
- Macrophages
Transplantation Immunology, 79-6497
- Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6299, 79-6517
- 79-6518
- Adenofibroma, 79-6299
- Dose-Response Study, Review
79-6070
- Neoplasm Transplantation, 79-6515
- Meningioma
Case Report, 79-6529
- Mouse, NBZ
Virus Activation, 79-6366
- Multiple Myeloma
Epidemiology, 79-6576
- Occupational Hazard, 79-6576
- Mutation
Drosophila melanogaster, 79-6365
- Risk Evaluation, Review, 79-6049
- 79-6068
- Neoplasms, Radiation-Induced
Dose-Response Study, Review
79-6070
- Neutrons
Cell Transformation, Neoplastic

Radiation, Ionizing (cont'd)
Cell Transformation, Neoplastic
79-6360

Pancreatic Neoplasms

Epidemiology, 79-6576

Occupational Hazard, 79-6576

Risk Factors

Statistical Analysis, 79-6578

Skin Neoplasms

Immunologic Deficiency Syndromes
79-6092

Smoking

Co-carcinogenic Effect, Review

79-6053

12-O-Tetradecanoylphorbol-13-acetate
Cell Transformation, Neoplastic

79-6361

Chromatids, 79-6361

Thyroid Neoplasms

Adenoma, 79-6113, 79-6368

Carcinoma, 79-6369

Carcinoma, Papillary, 79-6368

Dose-Response Study, Review

79-6070

Epidemiology, Review, 79-6113

Virus, Friend Murine Leukemia

Immunosuppression, 79-6408

Virus, Murine Leukemia

Precancerous Conditions, Review
79-6083

Radioactive Fallout

Alpha Particles

Theoretical Model, Review, 79-6070

Risk Factors

Statistical Analysis, 79-6578

Radon

Lung Neoplasms

Dose-Response Study, 79-6371

Epidemiology, 79-6371

Receptors, Hormone

Breast Neoplasms

Androgens, 79-6349

Carcinoma, 79-6349

Estrogens, 79-6346, 79-6347, 79-6349

Isolation and Characterization

79-6346

Progesterone, 79-6347, 79-6349

Prognosis, 79-6347

Estrogens

Cell Transformation, Neoplastic, Re-

view, 79-6031

Mammary Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-

79-6346

Estrogens, 79-6346

Progesterone, 79-6346

Urea, Methyl Nitroso-, 79-6346

Norepinephrine

Trifluoperazine, 79-6164

Steroids

Cell Differentiation, Review, 79-6019

Rectal Neoplasms

Alcoholic Beverages

Epidemiology, 79-6564

Respiratory Tract Neoplasms

Asbestos

Epidemiology, 79-6570

Epidemiology, Review, 79-6052

Occupational Hazard, 79-6570

Dipropylamine, 2-Hydroxy-N-nitroso-2'-

oxo-

Histological Study, Hamster, 79-6196

Environmental Hazard

Epidemiology, Spain, Review, 79-6111

Smoking

Epidemiology, Review, 79-6126

Retinoblastoma

Eye Neoplasms

Epidemiology, Sudan, 79-6554

Retinoic Acid

12-O-Tetradecanoylphorbol-13-acetate

Prostaglandins, 79-6277

Retinol

Aflatoxin B1

Metabolism, Review, 79-6019

Breast Neoplasms

Serum Levels, 79-6339

Zinc, 79-6339

Lung Neoplasms

Epidemiology, Review, 79-6026

Polycyclic Hydrocarbons

Metabolism, Review, 79-6019

Retinol Acetate

Mammary Neoplasms, Experimental

Urea, Nitroso-, 79-6200

Reverse Transcriptase

Glioblastoma Multiforme

Virus, RNA Tumor, 79-6459

Virus, Moloney Murine Sarcoma

DNA, Viral, 79-6413

Virus, Moloney Murine Sarcoma-

Leukemia

Thermosensitivity, 79-6414

Virus, Murine Leukemia

Replication Defective Mutants

79-6416

Virus, Helper, 79-6416

Rhabdomyosarcoma

Teratoid Tumor

Pineal Body, 79-6530

Vaginal Neoplasms

Epidemiology, Review, 79-6125

Rhodamine B

Ames Test

Mutagenic Activity, 79-6264

DNA

Strand Breaks, 79-6264

Rhodamine 6G

Ames Test

Mutagenic Activity, 79-6264

DNA

Strand Breaks, 79-6264

Ribonuclease

Ethane, 1,1,1-Trichloro-2,2-bis(p-

chlorophenyl)-

Patulin, 79-6257

Luteoskyrin

Enzyme Inhibition, 79-6257

Patulin

Enzyme Inhibition, 79-6257

Penicillium roqueforti

Mycotoxins, 79-6257

Rugulosin

Enzyme Inhibition, 79-6257

Virus, Avian Sarcoma

RNA, Viral, 79-6379

Ribonucleoproteins

Virus, Mengo

RNA, Viral, 79-6464

Ribosomes

Cycloheximide

Mutation, 79-6159

Neurospora crassa, 79-6159

Ricinus communis

Lymphoma

Plant Agglutinins, 79-6593

Rifampicin, Dihydro-

Virus, Rauscher Murine Leukemia

RNA Polymerase, 79-6402

RNA, Messenger

Cell Transformation, Neoplastic

Molecular Biology, Review, 79-6001

Dimethylamine, N-Nitroso-

Liver, Mouse, 79-6185

Teratoid Tumor

Virus, SV40, 79-6450

Virus, Adeno 2

DNA-RNA Hybridization, 79-6453

Peptides, 79-6454

Polyribosomes, 79-6453

Virus, Avian Sarcoma

RNA, Messenger (cont'd)

Glycoproteins, 79-6380

Membrane Proteins, 79-6380

Polyribosomes, 79-6380

RNA Polymerase

Ethane, 1,1,1-Trichloro-2,2-bis(p-

chlorophenyl)-

RNA Replication, 79-6257

2,5-Hexadienoic Acid, 3-Methoxy-5-

methyl-4-oxo-

RNA Replication, 79-6257

Luteoskyrin

RNA Replication, 79-6257

Patulin

RNA Replication, 79-6257

Penicillium roqueforti

Mycotoxins, 79-6257

Rugulosin

RNA Replication, 79-6257

Virus, Rauscher Murine Leukemia

Cell Transformation, Neoplastic

79-6402

Rifampicin, Dihydro-, 79-6402

RNA Replication

Ethane, 1,1,1-Trichloro-2,2-bis(p-

chlorophenyl)-

RNA Polymerase, 79-6257

2,5-Hexadienoic Acid, 3-Methoxy-5-

methyl-4-oxo-

RNA Polymerase, 79-6257

Luteoskyrin

RNA Polymerase, 79-6257

Patulin

RNA Polymerase, 79-6257

Rugulosin

RNA Polymerase, 79-6257

RNA, Ribosomal

Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-

Nucleotides, Binding, 79-6250

Estradiol

Genes, Embryonic, Review, 79-6030

Virus, SV40

Hybrid Cells, 79-6449

Nucleolus Organizer Region, 79-6449

RNA, Transfer Methyltransferases

Dimethylamine, N-Nitroso-

Polyribosomes, 79-6185

RNA, Viral

Virus, Adeno 2

Peptides, 79-6456

Viral Proteins, 79-6456

Virus, Avian Erythroblastosis

Cell Transformation, Neoplastic

79-6384

Viral Proteins, 79-6384

Virus, Helper, 79-6384

Virus, Avian Sarcoma

DNA Replication, 79-6379

Ribonuclease, 79-6379

Triton X 100, 79-6379

Virus, Gibbon Ape Lymphoma

Nucleotide Sequence, 79-6423

Virus, Mengo

Ribonucleoproteins, 79-6464

Virus, Murine Mammary Tumor

Dexamethasone, 79-6395

Virus, Simian Sarcoma

Nucleotide Sequence, 79-6423

Virus, Woolly Monkey Sarcoma

Nucleotide Sequence, 79-6423

Rubber

Solvents

Chromatids, 79-6238

Chromosome Aberrations, 79-6238

Rugulosin

Ribonuclease

Enzyme Inhibition, 79-6257

RNA Polymerase

RNA Replication, 79-6257

Saccharomyces cerevisiae

1,2-Benzisothiazolin-3-one, 1,1-Dioxide

Saccharomyces cerevisiae (cont'd)

- Mutagenic Activity, 79-6252
- DNA, Mitochondrial Mutation, 79-6152
- Ethidium Bromide Mutation, 79-6152
- Fluorescent Dyes
- Mutagenic Activity, Review, 79-6018
- Food Additives
- Mutagenic Activity, 79-6286
- Psoralen, 3-Carbethoxy-Mutation, 79-6152
- p*-Tolamide, *N*-Isopropyl- α -(2-methylhydrazino)-
- Mutagenic Activity, 79-6243

Salicylic Acid

- Gastritis
- Hemorrhage, 79-6550
- Peptic Ulcer
- Hemorrhage, 79-6550

Salmonella typhimurium

- Chlorophyllin A
- Growth, 79-6131
- Interferon
- Toxicity, 79-6463
- Sodium Azide
- Mutagenic Metabolite, 79-6144

Sarcoma

- Antigens, Neoplasm
- Immune Response, 79-6310
- Isolation and Characterization
- 79-6310
- 3,3'-Biphenyldicarboxylic Acid, 4,4'-Diamino-
- Carcinogenic Potential, Rat, 79-6251
- Carcinogen, Chemical
- Fetal Globulins, Review, 79-6081
- Cell Transformation, Neoplastic
- Dose-Response Study, 79-6499
- Cholanthrene, 3-Methyl-
- Antigens, Neoplasm, 79-6310
- T-Lymphocytes, 79-6502
- Complement
- Cytotoxicity Assay, 79-6500
- Contact Inhibition
- Cells, Cultured, Review, 79-6091
- Naphtho(1,8-gh:5,4-g'h')diquinoline
- Carcinogenic Activity, 79-6330
- Dibenzo(b,def)chrysene
- Carcinogenic Activity, 79-6330
- Hepatoma
- Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Hydroxylamine, *O*-Benzoyl-*N*-methyl-*N*-(*p*-phenylazo)phenyl-
- Carcinogenic Activity, Rat, 79-6246
- Hypothyroidism
- Neoplasm Metastasis, 79-6595
- Isoantibodies
- Hemolysis, 79-6500
- Killer Cells
- Ultrastructural Study, 79-6502
- Virus-Like Particles, 79-6502
- Lung Neoplasms
- Neoplasm Metastasis, 79-6534
- Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Membrane Proteins
- Neoplasm Metastasis, 79-6534
- Neurilemmoma
- Drug Therapy, 79-6211
- Nickel Sulfide
- Mouse, Nude, 79-6499
- Neoplasm Metastasis, 79-6142
- Transplantation Immunology, 79-6499
- X-Ray Diffraction and Autoradiographic Study, 79-6142
- Osteitis Deformans
- Epidemiology, 79-6588
- Parotid Neoplasms
- Propionic Acid, 2-(*p*-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6153
- Skull Neoplasms
- Osteitis Deformans, 79-6588
- Thyroxine

Sarcoma (cont'd)

- Neoplasm Metastasis, 79-6595
- Transplantation Immunology, 79-6595
- Toxaphene
- Carcinogenic Potential, Review
- 79-6003
- Mouse, Rat, Review, 79-6003
- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
- Drug Therapy, 79-6211
- Virus, Adeno 2
- Transplantation Immunology, 79-6501
- Virus, Adeno 2 - SV40 Hybrid
- DNA, Viral, 79-6458
- Virus, C-Type RNA Tumor
- Virus-Like Particles, 79-6502
- Virus, Rous Sarcoma
- Immunogenetics, 79-6498
- Virus, SV40
- Fetal Globulins, Review, 79-6081
- Water Pollutants
- Chloroform Extracts, 79-6344

Sarcoma 180, Crocker

- 1,3-Butadiene, 2-Chloro-
- Immune Response, Review, 79-6050

Sarcoma, Ewing's

- Bone Neoplasms
- Diagnosis and Prognosis, 79-6562
- Neoplasm Metastasis, 79-6562

Sarcoma, Mast Cell

- Butyric Acid, 2-Amino-4-(ethylthio)-
- DNA, Methylation, 79-6156
- Nucleotide Sequence, 79-6156
- DNA, Neoplasm
- DNA-RNA Hybridization, 79-6594
- Nucleotide Sequence
- Liver, Spleen, Rat, 79-6594

Sarcoma, Reticulum Cell

- Age Factors
- Epidemiology, 79-6579
- Antilymphocyte Serum
- Immunosuppression, 79-6009
- Azathioprine
- Immunosuppression, 79-6009
- Cyclophosphamide
- Immunosuppression, 79-6009
- Graft vs Host Reaction
- Morphological Study, Mouse, 79-6485
- Granuloma
- Histological Study, 79-6521
- Immunoblastic Lymphadenopathy
- Case Report, 79-6526
- Ultrastructural, Immunohistochemical
- Study, 79-6526
- Immunosuppression
- Transplantation, Homologous, 79-6009
- Virus, Radiation Leukemia
- Histological Study, 79-6399
- Organ Specificity, 79-6399

Sebaceous Gland Neoplasms

- Benz(a)anthracene, 7,12-Dimethyl-
- Oxidoreductases, 79-6302
- 4-Stilbenamine, *N,N*-Dimethyl-
- 79-6302
- Carcinoma
- Benz(a)anthracene, 7,12-Dimethyl-
- 79-6302
- Carcinoma, Epidermoid
- Benz(a)anthracene, 7,12-Dimethyl-
- 79-6302
- Lactate Dehydrogenase
- Zymbal Gland, Rat, 79-6302
- Malate Dehydrogenase
- Zymbal Gland, Rat, 79-6302

Serine, Diazoacetate (Ester)

- Pancreatic Neoplasms
- Carcinoma, 79-6508

Serotonin

- Prostatic Neoplasms
- Cholanthrene, 3-Methyl-, 79-6307
- Stomach Neoplasms
- Carcinoid Tumor, 79-6539

Sex Chromosomes

- Carbamic Acid, Ethyl Ester
- Drosophila melanogaster*, 79-6198
- Dimethylamine, *N*-Nitroso-
- Chromosome Aberrations, 79-6205
- Drosophila melanogaster*
- Mutation, 79-6365
- Electrons
- Food Contamination, 79-6364
- Fibrosarcoma
- Cholanthrene, 3-Methyl-, 79-6306
- Food Contamination
- Drosophila melanogaster*, 79-6364
- Methane, Sulfenylbis-
- Chromosome Aberrations, 79-6205
- Methanesulfonic Acid, Methyl Ester
- Chromosome Aberrations, 79-6205
- Radiation, Ionizing
- Drosophila melanogaster*, 79-6198
- Food Contamination, 79-6364
- Urea, Methyl Nitroso-
- Chromosome Aberrations, 79-6205

Sialic Acid

- Virus, Murine Sarcoma
- Cell Membrane, 79-6538
- Neuraminidase, 79-6538

Sialoglycoproteins

- Virus, Murine Sarcoma
- Neoplasm Metastasis, 79-6538

Silicon

- Macrophages
- Enzymes, Review, 79-6102

Silicosis

- Gold
- Occupational Hazard, 79-6585

Skin Neoplasms

- Acridine, 3,6-Diamino-
- Light, 79-6287
- Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-7,12-dimethyl-
- Benz(a)anthracene, 3,4-Dihydro-3,4-dihydroxy-7,12-dimethyl-, 79-6309
- 12-*O*-Tetradecanoylphorbol-13-acetate
- 79-6309
- Benz(a)anthracene, 7,12-Dimethyl-
- Carcinogenic Metabolite, 79-6309
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
- 79-6327
- Poly A-U, 79-6295
- Transplantation, Homologous, 79-6297
- Benzo(a)pyrene
- Benz(a)anthracene, 7,12-Dimethyl-
- 79-6327
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
- 7,8,9,10-tetrahydro-
- Nucleoside Adducts, 79-6327
- 1,3-Butadiene, 2-Chloro-
- Carcinogenic Potential, Review
- 79-6050
- Carcinoma, Epidermoid
- Chrysene, 6-Fluoro-5-methyl-, 79-6305
- Leukemia, Myeloblastic, 79-6520
- Cholanthrene-2-ol, 3-Methyl-
- 12-*O*-Tetradecanoylphorbol-13-acetate
- 79-6308
- Cholanthrene-2-one, 3-Methyl-
- 12-*O*-Tetradecanoylphorbol-13-acetate
- 79-6308
- Cholanthrene, 9,10-Dihydro-9,10-dihydroxy-3-methyl-
- 12-*O*-Tetradecanoylphorbol-13-acetate
- 79-6309
- Cholanthrene, 9,10-Dihydro-3-methyl-
- 1,9,10-trihydroxy-
- 12-*O*-Tetradecanoylphorbol-13-acetate
- 79-6308
- Cholanthrene, 3-Methyl-
- Carcinogenic Metabolite, 79-6309
- Coumarin
- Carcinogenic Potential, Review
- 79-6066
- Diol Epoxides
- Phenanthrene, 3,4-Epoxy-1,2,3,4-

Skin Neoplasms (cont'd)

- tetrahydro-, 79-6304
- Fibrosarcoma
 - Propionic Acid, 2-(p-Chlorophenoxy)-2-methyl-, Ethyl Ester, 79-6154
- Immunologic Deficiency Syndromes
 - Chromosome Aberrations, Review 79-6092
- Leukemia, Lymphocytic
 - Immune Response, 79-6473
- Lymphosarcoma
 - Immune Response, 79-6473
- Mammary Neoplasms, Experimental
 - Ultraviolet Rays, 79-6287
- Melanoma
 - Strain Difference, Hamster, 79-6544
- Neoplasms, Embryonal and Mixed
 - Ultrastructural Study, 79-6535
- Neutral Red
 - Light, 79-6287
- Papilloma
 - Benz(a)anthracene, 7,12-Dimethyl-79-6295
 - Chrysene, 1,2-Dihydro-, 79-6304
- Piper nigrum*
 - Carcinogenic Potential, 79-6258
- Psoralen, 8-Methoxy-
 - Photochemotherapy, Review, 79-6071
- Radiation, Ionizing
 - Immunologic Deficiency Syndromes 79-6092
- Ultraviolet Rays
 - Immunologic Deficiency Syndromes 79-6092
 - Photochemotherapy, Review, 79-6071
- Xeroderma Pigmentosum
 - DNA Repair, Review, 79-6067

Skull Neoplasms

- Sarcoma
 - Osteitis Deformans, 79-6588

Smoke Condensate

- Adrenal Gland Neoplasms
 - Hyperplasia, 79-6285
- Aromatic Amines
 - Quantitation Method, 79-6241
- Benzo(a)pyrene
 - Mutagenic Activity, Review, 79-6016
- Gynecologic Neoplasms
 - Transplacental, Neonatal Carcinogenesis, 79-6285
- Liver Neoplasms
 - Hyperplasia, 79-6285
- Transplacental, Neonatal Carcinogenesis, 79-6285
- Pancreatic Neoplasms
 - Transplacental, Neonatal Carcinogenesis, 79-6285

Smoking

- Asbestos
 - Co-carcinogenic Effect, Review 79-6052, 79-6054
- Bladder Neoplasms
 - Epidemiology, Iran, 79-6581
 - Tars, 79-6584
- Environmental Hazard
 - Risk Factors, 79-6578
- Esophageal Neoplasms
 - Carcinoma, 79-6566
 - Epidemiology, 79-6565
 - Epidemiology, Review, 79-6126
- Imidazole-1-ethanol, 2-Methyl-5-nitro-
 - Co-carcinogenic Effect, 79-6217
- Laryngeal Neoplasms
 - Carcinoma, 79-6284
 - Inhalation Study, Hamster, 79-6284
 - Tobacco Substitutes, 79-6284
- Lung Neoplasms
 - Epidemiology, Australia, 79-6585
 - Epidemiology, Bombay, 79-6583
 - Epidemiology, Review, 79-6053
 - Tars, 79-6584
- Mesothelioma
 - Epidemiology, Review, 79-6104
- Mouth Neoplasms
 - Leukoplakia, Oral, 79-6531

Smoking (cont'd)

- Nickel
 - Co-carcinogenic Effect, Review 79-6054
- Pancreatic Neoplasms
 - Epidemiology, Review, 79-6126
- Polycyclic Hydrocarbons
 - Co-carcinogenic Effect, Review 79-6113
- Respiratory Tract Neoplasms
 - Epidemiology, Review, 79-6126
- Urologic Neoplasms
 - Epidemiology, Review, 79-6126
- Sodium
 - Hepatoma
 - Amino Acids, 79-6598
- Sodium Azide
 - Ames Test
 - Mutagenic Metabolite, 79-6144
 - S9 Fraction, 79-6157
 - Lymphoma
 - Cell Aggregation, 79-6593
 - Salmonella typhimurium*
 - Mutagenic Metabolite, 79-6144
- Sodium Fluoride
 - Lymphoma
 - Cell Aggregation, 79-6593
- Soft Tissue Neoplasms
 - Benzo(a)pyrene
 - Cholesterol, 14-Methylhexadecanoate 79-6338
 - Fibroma
 - Anthraquinone, 2-Methyl-1-nitro-79-6262
- Solvents
 - Benzene
 - Chromosome Aberrations, 79-6238
 - Paraffin Oil
 - Chromosome Aberrations, 79-6238
 - Rubber
 - Chromatids, 79-6238
 - Chromosome Aberrations, 79-6238
- Somatotropin
 - Progestational Hormones
 - Pharmacokinetics, 79-6352
 - Uterine Neoplasms
 - Pharmacokinetics, 79-6352
- Somatotropin Release Inhibiting Hormone
 - Stomach Neoplasms
 - Carcinoid Tumor, 79-6539
- Spermatozoa
 - Fosfestrol
 - Mutagenic Activity, 79-6239
- Spinal Cord Neoplasms
 - Astrocytoma
 - Urea, Ethyl Nitroso-, 79-6210
 - Glioma
 - Urea, Ethyl Nitroso-, 79-6210
 - Lipoma
 - Cauda Equina, 79-6555
 - Epidemiology, Child, 79-6555
 - Oligodendroglioma
 - Urea, Ethyl Nitroso-, 79-6210
 - Urea, Ethyl Nitroso-
 - Transplacental, Postnatal Exposure, Rat, 79-6210
- Spleen
 - Leukemia, Lymphocytic
 - Neoplasm Circulating Cells, 79-6469
- Staphylococcus aureus*
 - Nitroso Compounds
 - Co-carcinogenic Effect, Review 79-6057
- Steroids
 - Aflatoxin B1
 - Chromosomes, Review, 79-6019
 - Gastrointestinal Neoplasms
 - Epidemiology, Review, 79-6101
 - Polycyclic Hydrocarbons

Steroids (cont'd)

- Chromosomes, Review, 79-6019
- Receptors, Hormone
 - Cell Differentiation, Review, 79-6019
- Structure-Activity Relationship
 - Ames Test, Review, 79-6023
- 4-Stilbenamine, N,N-Dimethyl-
 - Blood Proteins
 - Metabolism, Rat, 79-6340
 - Ear Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-79-6302
 - Nucleic Acids
 - Dose-Response Study, Binding 79-6340
 - Liver, Rat, 79-6340
 - Proteins
 - Dose-Response Study, Binding 79-6340
 - Liver, Rat, 79-6340
 - Sebaceous Gland Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-79-6302
 - Structure-Activity Relationship
 - Epoxide Metabolite, Review, 79-6024
- trans-Stilbene Oxide
 - Benzo(a)pyrene
 - Ames Test, 79-6316
 - Carcinogenic Metabolite, 79-6316
 - Benzo(a)pyrene 4,5-Oxide
 - Epoxide Hydratases, 79-6316
 - Epoxide Hydratases
 - Liver, Rat, 79-6316
 - Oxidoreductases
 - Liver, Rat, 79-6316
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Abnormalities
 - Epidemiology, Review, 79-6025
 - Adenocarcinoma
 - Epidemiology, Review, 79-6025
 - Gynecologic Neoplasms
 - Transplacental Carcinogenesis, Review 79-6025
 - Testicular Neoplasms
 - Transplacental Carcinogenesis, Review 79-6025
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Ames Test
 - Carcinogenic Metabolite, 79-6341
 - 7,8-Benzoflavone
 - Chromatids, 79-6341
 - Carcinogen, Environmental
 - Experimental Toxicology, Review 79-6104
 - Carcinogenic, Mutagenic Activity
 - Bioassays, Review, 79-6048
 - Chromatids
 - Chromosome Aberrations, 79-6341
 - Fibroblasts, 79-6341
 - β -Dienestrol
 - Chromatids, 79-6341
 - DNA, Binding
 - Liver, Rat, Review, 79-6021
 - Gynecologic Neoplasms
 - Metaplasia, 79-6342
 - Ultrastructural Study, Mouse, 79-6342
 - Peroxidases
 - Metabolism, 79-6024
 - Structure-Activity Relationship
 - Epoxide Metabolite, Review, 79-6024
 - Vaginal Neoplasms
 - Adenocarcinoma, 79-6125
- 4,4'-Stilbenediol, α,α' -Diethyl-, α,β -Oxide
 - Chromatids
 - Fibroblasts, 79-6341
- Stomach Neoplasms
 - Achlorhydria
 - Epidemiology, 79-6561
 - Adenocarcinoma
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-79-6221, 79-6222, 79-6223
 - Propionic Acid, 2-(p-Chlorophenoxy)-

Stomach Neoplasms (cont'd)
 2-methyl-, Ethyl Ester, 79-6153
Adenoma
 Classification, Review, 79-6094
 Guanidine, 1-Methyl-3-nitro-1-nitroso-79-6222
Carcinoembryonic Antigen
 Precancerous Conditions, 79-6512
Carcinoid Tumor
 Gastrin, 79-6539
 Immunohistochemical Study, Masts, 79-6539
 Serotonin, 79-6539
 Somatotropin Release Inhibiting Hormone, 79-6539
Carcinoma
 Gastrectomy, 79-6512
 Hydroxylamine, *N*-methyl-*N*-(*p*-(phenylazo)phenyl)-, 79-6246
Carcinoma In Situ
 Classification, Review, 79-6094
DNA Replication
 Neoplasm Invasiveness, 79-6221
Gastrectomy
 Epidemiology, 79-6561
 Precancerous Conditions, Review 79-6094
Genetics
 Epidemiology, 79-6561
Glutathione
 Carcinogenic Metabolite, 79-6219
 Guanidine, 1-Methyl-3-nitro-1-nitroso-Glutathione, 79-6219
 Precancerous Conditions, 79-6222
Metaplasia
 Precancerous Conditions, Review 79-6094
Papilloma
 Hydroxylamine, *N*-methyl-*N*-(*p*-(phenylazo)phenyl)-, 79-6246
Polyps
 Precancerous Conditions, Review, 79-6094
Strontium
 Virus, Friend Murine Leukemia
 Neoplasm Regression, Spontaneous 79-6408
Styrene
Drosophila melanogaster
 Mutagenic Activity, 79-6248
Succinic Acid, Disodium Salt
 Carcinoma, Ehrlich Tumor
 Karyotyping, 79-6536
Sulfide, Bis(2-chloroethyl)-
 Carcinogen, Environmental
 Experimental Toxicology, Review 79-6104
Smoking
 Co-carcinogenic Effect, Review 79-6053
Sulfuric Acid, Iron Salt
 Benz(a)anthracene-7-methanol, 12-Methyl-
 Oxidation Products, 79-6289
 Benzo(a)pyrene
 Dihydrodiol Metabolites, 79-6333
Surgery, Operative
 Intestinal Neoplasms
 Enterectomy, 79-6378
 Methane, Azoxy-, 79-6378
Synovioma
 Nerve Tissue
 Histological Study, 79-6527
Talc
 Ovarian Neoplasms
 Occupational Hazard, Review, 79-6123
 Vaginal Preparations
 Carcinogenic Potential, Review 79-6055
Tars
 Bladder Neoplasms

Tars (cont'd)
 Smoking, 79-6584
 Lung Neoplasms
 Smoking, 79-6584
 Tobacco
 Respiratory Tract Distribution 79-6284
Teratoid Tumor
 Alpha Fetoproteins
 Cell Differentiation, Review, 79-6089
 Chromosomes
 Cell Differentiation, Review, 79-6089
 Rhabdomyosarcoma
 Pineal Body, 79-6530
 Testicular Neoplasms
 Virus, AKR Murine Leukemia 79-6406
 Virus, AKR Murine Leukemia
 Cell Differentiation, 79-6406
 Virus Replication, 79-6406
 Virus, SV40
 Antigens, Neoplasm, 79-6450
 Cell Differentiation, 79-6075
 Cell Line, Review, 79-6075
 RNA, Messenger, 79-6450
 Virus Replication, 79-6450
Testicular Neoplasms
 Leydig Cell Tumor
 FSH, 79-6351
 Imidazole-1-ethanol, 2-Methyl-5-nitro-79-6216
 LH, 79-6351
 4,4'-Stilbenediol, α,α' -Diethyl-
 Transplacental Carcinogenesis, Review 79-6025
Teratoid Tumor
 Virus, AKR Murine Leukemia 79-6406
Testosterone
 Mammary Neoplasms, Experimental
 Carcinogenic Potential, Dog, 79-6352
 Prostatic Neoplasms
 Adenocarcinoma, 79-6351
 Carcinoma, Epidermoid, 79-6307
12-O-Tetradecanoylphorbol-13-acetate
 Anthranilic Acid, *N*-(α,α,α -Trifluoro-*m*-tolyl)-
 Prostaglandins E, 79-6274
 Cell Transformation, Neoplastic
 Trachea, Rat, 79-6276
 Cycloheximide
 5,8,11,14-Eicosatetranoic Acid 79-6277
 DNA Replication
 Lymphocyte Culture Test, Mixed 79-6270
 5,8,11,14-Eicosatetranoic Acid
 Fibroblasts, Chick Embryo, 79-6277
 Erythrocytes
 5,8,11,14-Eicosatetranoic Acid 79-6278
 Prostaglandins E, 79-6278
 Prostaglandins F, 79-6278
 Virus, Friend Murine Leukemia 79-6278
 Fibroblasts
 Cell Differentiation, 79-6271
 Indole-1-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-
 Prostaglandins, 79-6277
 Prostaglandins E, 79-6274
 Lymphocyte Transformation
 Suppressor Cells, 79-6270
 Ultrastructural Study, 79-6269
 Lymphocytes
 Agglutination, 79-6269
 Melanoma
 Melanin, 79-6268
 Mitomycin C
 Chromatids, 79-6273
 Muscles
 Cell Differentiation, 79-6271
 Myofibrils

12-O-Tetradecanoylphorbol-13-acetate (cont'd)
 Cell Differentiation, 79-6271
 2-Naphthaleneacetic Acid, 6-Methoxy- α -methyl-
 Prostaglandins E, 79-6274
 Ornithine Decarboxylase
 Cell Division, 79-6275
 Tumor Promoting Activity, 79-6275
 Platelet Aggregation
 Prostaglandin Synthase, 79-6272
 Vasoactive Material, 79-6272
 Prostaglandins E
 Epidermis, Mouse, 79-6274
 Fibroblasts, Chick Embryo, 79-6277
 Prostaglandins F
 Epidermis, Mouse, 79-6274
 Fibroblasts, Chick Embryo, 79-6277
 Puromycin
 5,8,11,14-Eicosatetranoic Acid 79-6277
 Putrescine
 Epidermis, Mouse, 79-6275
 Radiation, Ionizing
 Cell Transformation, Neoplastic 79-6361
 Chromatids, 79-6361
 Retinoic Acid
 Prostaglandins, 79-6277
 Skin Neoplasms
 Benz(a)anthracene, 3,4-Dihydro-3,4-dihydroxy-7,12-dimethyl-, 79-6309
 Cholanthen-2-ol, 3-Methyl-, 79-6308
 Cholanthen-2-one, 3-Methyl-79-6308
 Cholanthrene, 9,10-Dihydro-9,10-dihydroxy-3-methyl-, 79-6309
 Cholanthrene, 9,10-Dihydro-3-methyl-1,9,10-trihydroxy-, 79-6308
 Uridine, 5-Bromo-2'-deoxy-
 Chromatids, 79-6273
 Virus, Epstein-Barr
 Antigens, Viral, 79-6431
 Virus Activation, 79-6428
Theca Cell Tumor
 Ovarian Neoplasms
 Epidemiology, Dog, 79-6121
Theophylline
 Benz(a)anthracene, 7,12-Dimethyl-DNA, Binding, 79-6294
Thiazolidine-4-carboxylic Acid, 2-Oxo-
 Metabolism
 Liver, Rat, 79-6149
Thiiraneacetoneitrile
 DNA, Binding
 Liver, Rat, Review, 79-6021
Thiocyanic Acid
 Nitroso Compounds
 Co-carcinogenic Effect, Review 79-6057
Thiram
 see Disulfide, Bis(dimethylthiocarbamoyl)-
Thymidine
 Tritium
 Transplacental Carcinogenesis 79-6266
Thymoma
 Virus, Murine Leukemia
 Antigenic Determinants, 79-6083
 Precancerous Conditions, Review 79-6083
Thymosine
 see *D*-erythro-Pentose, 2-Deoxy-
Thymus Gland
 Virus, Friend Murine Leukemia
 Neoplasm Regression, Spontaneous 79-6408

Thymus Neoplasms
Lymphosarcoma
Virus, Radiation Leukemia, 79-6399

Thyroid Neoplasms
Adenoma
Radiation, Ionizing, 79-6113, 79-6368
Strain Difference, Hamster, 79-6544
Adenomatosis, Familial Endocrine
Genetics, Review, 79-6093
Carcinoma
Radiation, Ionizing, 79-6369
Carcinoma, Papillary
Radiation, Ionizing, 79-6368
Hodgkin's Disease
Radiotherapy, 79-6369
Medulloblastoma
Radiotherapy, 79-6368
Neutral Red
Light, 79-6287
Radiation, Ionizing
Dose-Response Study, Review
79-6070
Epidemiology, Review, 79-6113
Water Pollutants
Chloroform Extracts, 79-6343

Thyroxine
Fibrosarcoma
Neoplasm Metastasis, 79-6595
Transplantation Immunology, 79-6595
Sarcoma
Neoplasm Metastasis, 79-6595
Transplantation Immunology, 79-6595

Tobacco
Mouth Neoplasms
Epidemiology, Review, 79-6099
Tars
Respiratory Tract Distribution
79-6284

**p-Toluamide, N-Isopropyl- α -(2-methyl-
ONN-azoxy)-**
Microsomes, Liver
Oxidative Metabolism, 79-6244

p-Toluamide, N-Isopropyl- α -(2-methylazo)-
Microsomes, Liver
Oxidative Metabolism, 79-6244

p-Toluamide, N-Isopropyl- α -(2-methylhydrazino)-
Ames Test
Mutagenic Activity, 79-6243
Benzamide, p-Formyl-N-isopropyl-
Microsomes, Liver, 79-6244
Hydrazine, Methyl-
Microsomes, Liver, 79-6244
Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6299
Microsomes, Liver
Oxidative Metabolism, 79-6244
Saccharomyces cerevisiae
Mutagenic Activity, 79-6243

Toluene-2,4-diamine
Hepatoma
Histological Study, Mouse, 79-6240
Precancerous Conditions, 79-6240

m-Toiuidine, N,N-Dimethyl-4-(phenylazo)-
Microsomes, Liver
Ames Test, 79-6242

m-Toiuidine
Smoke Condensate
Aromatic Amines, 79-6241

o-Toiuidine
Smoke Condensate
Aromatic Amines, 79-6241

p-Toiuidine
Smoke Condensate
1-Naphthylamine, 4-Methyl-, 79-6241

Toxaphene
Ames Test
Mutagenic Activity, Review, 79-6002
Gynecologic Neoplasms

Toxaphene (cont'd)
Carcinogenic Potential, Review
79-6003
Mouse, Rat, Review, 79-6003
Liver Neoplasms
Mouse, Rat, Review, 79-6003
Mammary Neoplasms, Experimental
Carcinogenic Potential, Review
79-6003
Mouse, Rat, Review, 79-6003
Sarcoma
Carcinogenic Potential, Review
79-6003
Mouse, Rat, Review, 79-6003

Transferrin
Hepatoma
Cells, Cultured, 79-6597

Transformation, Genetic
Agrobacterium tumefaciens
DNA, Bacterial, 79-6037
Virus, Harvey Murine Sarcoma
DNA, Viral, 79-6410
Virus, Polyoma
DNA, Viral, 79-6434
Virus, SV40
DNA, Bacterial, 79-6442

Transplantation, Heterologous
Nasopharyngeal Neoplasms
Virus, Epstein-Barr, 79-6428
Pancreatic Neoplasms
Carcinoma, 79-6508
Carcinoma, Ductal, 79-6508

Transplantation, Homologous
Fibrosarcoma
Benz(a)anthracene, 7,12-Dimethyl-
79-6297
Corynebacterium parvum, 79-6493
Neoplasm Metastasis, 79-6493
Radiation, Ionizing, 79-6493
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6297

Transplantation Immunology
Carcinogen, Chemical
Fetal Globulins, Review, 79-6081
Fibrosarcoma
Benz(a)anthracene, 7,12-Dimethyl-
79-6497
Cyclophosphamide, 79-6161
Radiation, Ionizing, 79-6363
Thyroxine, 79-6595
Leukemia L1210
Virus, Sendai, 79-6479
Macrophages
Fetal Globulins, 79-6497
Radiation, Ionizing, 79-6497
Mammary Neoplasms, Experimental
Histocompatibility Antigens, 79-6514
Neoplasms, Experimental
Mouse, Review, 79-6086
Oncogenic Viruses
Fetal Globulins, Review, 79-6081
Sarcoma
Nickel Sulfide, 79-6499
Thyroxine, 79-6595
Virus, Adeno 2, 79-6501
Virus, Adeno 2
Age Factors, 79-6501
Virus, Rous Sarcoma
Histocompatibility Antigens, 79-6498
Virus, Sendai
Temperature Sensitive Mutants
79-6479
Virus, SV40
Histocompatibility Antigens, 79-6448

Triazene, 3,3-Dimethyl-1-phenyl-
Mutagenic Metabolite
Tissue Specificity, 79-6165

s-Triazoio(3,4-a)phthalazine-3-methanol
Ames Test
Mutagenic Activity, 79-6254

Trichomonas vaginalis
Cervix Neoplasms
Carcinoma In Situ, 79-6217

Trifluoperazine
Norepinephrine
Receptors, Hormone, 79-6164

Triglycerides
Carbon Tetrachloride
Liver, Rat, 79-6147
Isopropyl Alcohol
Liver, Rat, 79-6147
Methanol
Liver, Rat, 79-6147

Tritium
Chromatids
Chromosome Aberrations, 79-6353
Lymphocytes, 79-6353
Liver Neoplasms
Phorbol, 79-6266
Lung Neoplasms
Phorbol, 79-6266
Thymidine
Transplacental Carcinogenesis
79-6266
Uridine
Chromatids, 79-6353

Triton X 100
Virus, Avian Sarcoma
RNA, Viral, 79-6379

Trypan Blue
Carcinoma, Ehrlich Tumor
Antibody-Dependent Cell Cytotoxicity
79-6488
Immunity, Cellular, 79-6488
Complement
Cell Membrane, 79-6488

UDP Glucuronosyltransferase
Benzo(a)pyrene
Cells, Cultured, 79-6328

Ultraviolet Rays
Adenocarcinoma
Psoralen, 8-Methoxy-, 79-6287
Arginine
Chromosome Aberrations, 79-6224
Caffeine
DNA Repair, 79-6358
Carcinogen, Chemical
Quasi-Valence Number, 79-6128
Carcinosarcoma
Mammary Neoplasms, Experimental
79-6287
Chromatids
Cell Division, 79-6224
Lymphocytes, 79-6359
Dermatitis, Contact
DNA Repair, 79-6354
DNA Repair
Lymphocytes, 79-6358
Mutation, Review, 79-6067
Dwarfism
DNA Repair, 79-6377
Fibrosarcoma
Immunity, Cellular, 79-6494
Fluorene, 2-Azido-
Cytotoxicity, 79-6139
Fluorene, 2,5-Diazido-
Cell Transformation, Neoplastic
79-6139
Fluorene, 2,7-Diazido-
Cell Transformation, Neoplastic
79-6139
Lymphoma
Psoralen, 8-Methoxy-, 79-6287
Mammary Neoplasms, Experimental
Psoralen, 8-Methoxy-, 79-6287
Melanoma
Epidemiology, 79-6556
Mutation
Yeasts, 79-6191
Porphyria
DNA Repair, 79-6354
DNA Replication, 79-6354

Ultraviolet Rays (cont'd)
 Psoralen, 8-Methoxy-
 Chromatids, 79-6359
 Co-carcinogenic Effect, Review
 79-6071
Skin Neoplasms
 Immunologic Deficiency Syndromes
 79-6092
 Mammary Neoplasms, Experimental
 79-6287
 Photochemotherapy, Review, 79-6071
Virus, Adeno 2
 Transformation, 79-6458
Virus, Adeno 2 - SV40 Hybrid
 DNA, Viral, 79-6458
Virus, Herpes Simplex 1
 Virus Reactivation, 79-6377
Virus, Murine Leukemia
 Virus Activation, 79-6392
Virus, Murine Sarcoma
 Virus, Helper, 79-6392
Virus, SV40
 Cell Transformation, Neoplastic
 79-6356
 DNA Repair, 79-6356
 Xeroderma Pigmentosum
 DNA Repair, 79-6067, 79-6354
 79-6355, 79-6356, 79-6357

Uranium
 Lung Neoplasms
 Occupational Hazard, 79-6371

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Neoplasms, Multiple Primary
 Carcinogenic Activity, Rat, 79-6211
 Oligodendroglioma
 Drug Therapy, 79-6211
 Sarcoma
 Drug Therapy, 79-6211

Urea, 1-Butyl-1-nitroso-
Escherichia coli
 Mutagenic Activity, 79-6206

Urea, 1-(2-Chloroethyl)-3-(2-
 hydroxyethyl)-1-nitroso-
 Adenocarcinoma
 Drug Therapy, 79-6211
 Carcinoma
 Drug Therapy, 79-6211
 Cholangioma
 Drug Therapy, 79-6211
 Neoplasms, Multiple Primary
 Carcinogenic Activity, Rat, 79-6211

Urea, Ethyl Nitroso-
 Chromosome Aberrations
 Diethylamine, *N*-Nitroso-, 79-6209
Drosophila melanogaster, 79-6205
Escherichia coli
 Mutagenic Activity, 79-6206
 Spinal Cord Neoplasms
 Astrocytoma, 79-6210
 Glioma, 79-6210
 Oligodendroglioma, 79-6210
 Transplacental, Postnatal Exposure,
 Rat, 79-6210

Urea, Methyl Nitroso-
 Bladder Neoplasms
 Cell Membrane, 79-6203
 Precancerous Conditions, 79-6203
 Chromosome Aberrations
Drosophila melanogaster, 79-6205
 79-6209
 Sex Chromosomes, 79-6205
Colonic Neoplasms
 Adenocarcinoma, 79-6208
 Adenoma, 79-6208
 5 β -Cholan-24-oic Acid, 3 α ,7 α -
 Dihydroxy-, 79-6208
 Dietary Fiber, 79-6204
DNA
 Antinuclear Factors, 79-6466
 T-Lymphocytes, 79-6466
Escherichia coli
 Mutagenic Activity, 79-6206
 HeLa Cells

Urea, Methyl Nitroso- (cont'd)
 DNA Repair, 79-6466
 Liver Neoplasms
 DNA Repair, Review, 79-6065
 Mammary Neoplasms, Experimental
 Receptors, Hormone, 79-6346
 Purine, 2-Amino-6-methoxy-
 DNA Repair, Review, 79-6065
 Pyrazole
 Toxicity, Rat, 79-6148

Urea, (4-Nitrophenyl)-
 Ames Test
 Nitrosamides, 79-6202

Urea, Nitroso-
 Brain Neoplasms
 Ependymoma, 79-6201
 Glioma, 79-6201
 Oligodendroglioma, 79-6201
 Glioma
 Nucleic Acids, 79-6201
 Mammary Neoplasms, Experimental
 Retinol Acetate, 79-6200

Urea, *N*-Nitroso-*N*-propyl-
Escherichia coli
 Mutagenic Activity, 79-6206

Uridine
 Tritium
 Chromatids, 79-6353

Uridine, 5-Bromo-2'-deoxy-
 Chromatids
 Cell Cycle Kinetics, 79-6226
 Chromosome Aberrations, 79-6225
 Lymphocytes, 79-6225
 12-*O*-Tetradecanoylphorbol-13-acetate
 Chromatids, 79-6273
Virus, Murine Leukemia
 Virus Activation, 79-6392
Uridine, 2'-Deoxy-5-fluoro-
 Mutation
Drosophila melanogaster, 79-6365

Uridine, 2'-Deoxy-5-iodo-
 Virus, Epstein-Barr
 Virus Activation, 79-6428
Virus, Murine Leukemia
 Virus Activation, 79-6392

Urogenital Neoplasms
 Adenocarcinoma
 Propionic Acid, 2-(*p*-Chlorophenoxy)-
 2-methyl-, Ethyl Ester, 79-6153
 3,3'-Biphenyldicarboxylic Acid, 4,4'-
 Diamino-
 Carcinogenic Potential, Rat, 79-6251
 Carcinoma, Papillary
 Propionic Acid, 2-(*p*-Chlorophenoxy)-
 2-methyl-, Ethyl Ester, 79-6153
 Dipropylamine, 2-Hydroxy-*N*-nitroso-2'-
 oxo-
 Histological Study, Hamster, 79-6196
 Environmental Hazard
 Epidemiology, Spain, Review, 79-6111
 Intestinal Neoplasms
 Epidemiology, 79-6558

Urologic Neoplasms
 Smoking
 Epidemiology, Review, 79-6126

Uterine Neoplasms
 Adenocarcinoma
 Adenosine, Methyl Nitroso-, 79-6232
 Case Report, Ovariectomy, 79-6552
 Contraceptives, Oral, 79-6577
 Estrogens, 79-6567, 79-6577
 Estrone, 79-6028
 FSH, 79-6552
 LH, 79-6552
 Progesterone, 79-6028
 Receptors, Hormone, Review, 79-6028
 Diabetes Mellitus
 Drug Therapy, 79-6568
 Digitalis
 Drug Therapy, 79-6568

Uterine Neoplasms (cont'd)
 Estrogens
 Dietary Fats, Review, 79-6029
 Epidemiology, Finland, 79-6568
 Epidemiology, Review, 79-6124
 Menopause, 79-6348
 Hyperplasia
 Precancerous Conditions, Review
 79-6124

Hypertension
 Epidemiology, Israel, 79-6567
Menopause
 Epidemiology, Review, 79-6124
 Neoplasms, Multiple Primary
 Genetics, 79-6540

Obesity
 Epidemiology, Finland, 79-6568
 Epidemiology, Israel, 79-6567
 Progesterone, 79-6348
 Progesterone, 17 α -Hydroxy-
 Pharmacokinetics, 79-6352
Prolactin
 Dietary Fats, Review, 79-6029
 Somatotropin
 Pharmacokinetics, 79-6352

Vaginal Neoplasms
 Adenocarcinoma
 Epidemiology, Review, 79-6125
 4,4'-Stilbenediol, α,α' -Diethyl-
 79-6125

Carcinoma, Epidermoid
 Epidemiology, Review, 79-6125
 Neoplasm Metastasis, Review, 79-6125
Rhabdomyosarcoma
 Epidemiology, Review, 79-6125

Valeric Acid, 2,2-Diphenyl-, 2-(Di-
 ethylamino)ethyl Ester
 Dibenz(a,h)anthracene
 Aryl Hydrocarbon Hydroxylases
 79-6313

Ethane, 1,2-Dibromo-
 Macromolecules, Binding, 79-6150

Vinblastine Sulfate
 Cytochalasin B
 Cell Aggregation, 79-6593
 Lymphoma
 Plant Agglutinins, 79-6593

Viral Proteins
 Virus, Abelson Murine Leukemia
 Cell Membrane, 79-6403
 Virus, Helper, 79-6401
Virus, Adeno 2
 Arginine, 79-6457
 DNA, Binding, 79-6451, 79-6452
 RNA, Viral, 79-6456
 Tryptic Peptides, 79-6451, 79-6452
Virus, Avian Erythroblastosis
 RNA, Viral, 79-6384
Virus, Avian Sarcoma
 Cell Transformation, Neoplastic
 79-6382
 Protein Kinase, 79-6382
Virus, Bovine Papilloma
 Antibody Specificity, 79-6420
Virus, C-Type RNA Tumor
 Antigenic Determinants, 79-6460
 Radioimmunoassay, 79-6460
Virus, Mengo
 Isolation and Characterization
 79-6464
 Virus Assembly, 79-6464
Virus, Murine Mammary Tumor
 Radioimmunoassay, Milk, 79-6398

Virus, Abelson Murine Leukemia
 Immune Serums
 Antigen-Antibody Reactions, 79-6403
Viral Proteins
 Cell Membrane, 79-6403
Virus, Helper
 Transformation Defective Mutants
 79-6401
 Viral Proteins, 79-6401

Virus, Abelson Murine Leukemia (cont'd)
Virus, Moloney Murine Leukemia
Antigenic Determinants, 79-6403

Virus Activation
Oncogenic Viruses
Bacteria, 79-6463
Hamster, Review, 79-6079
Radiation, Ionizing
Mouse, NBZ, 79-6366
Virus, Epstein-Barr
12-O-Tetradecanoylphorbol-13-acetate
79-6428
Uridine, 2'-Deoxy-5-iodo-, 79-6428
Virus, Murine Leukemia
Ultraviolet Rays, 79-6392
Uridine, 5-Bromo-2'-deoxy-, 79-6392
Uridine, 2'-Deoxy-5-iodo-, 79-6392

Virus, Adeno
Carcinogen, Chemical
Focus Formation Assay, 79-6036

Virus, Adeno 2
Arginine
Peptide Hydrolases, 79-6457
Viral Proteins, 79-6457
DNA, Viral
Cleavage Sites, 79-6391
Endonucleases, 79-6391
T-Lymphocytes
Immunity, Cellular, 79-6501
Peptide Hydrolases
Isolation and Characterization
79-6455
Temperature Sensitive Mutants
79-6455
Peptides
Amino Acids, 79-6454
Cell Transformation, Neoplastic
79-6454
RNA, Messenger, 79-6454
RNA, Messenger
DNA-RNA Hybridization, 79-6453
Polyribosomes, 79-6453
RNA, Viral
Peptides, 79-6456
Viral Proteins, 79-6456
Sarcoma
Transplantation Immunology, 79-6501
Transplantation Immunology
Age Factors, 79-6501
Ultraviolet Rays
Transformation, 79-6458
Viral Proteins
DNA, Binding, 79-6451, 79-6452
Tryptic Peptides, 79-6451, 79-6452
Virus, Adeno Mouse FL
Nucleic Acid Homology, 79-6391

Virus, Adeno Mouse FL
DNA, Viral
Cleavage Sites, 79-6391
Endonucleases, 79-6391
Virus, Adeno 2
Nucleic Acid Homology, 79-6391

Virus, Adeno 2 - SV40 Hybrid
Fibrosarcoma
DNA, Viral, 79-6458
Sarcoma
DNA, Viral, 79-6458
Ultraviolet Rays
DNA, Viral, 79-6458

Virus, AKR Murine Leukemia
Anti-Antibodies
Genetics, 79-6404
Genetics
Virus Replication, 79-6405
Leukemia
Histocompatibility Antigens, 79-6477
Lymphoma
Crosses, Genetic, 79-6404
Teratoid Tumor
Cell Differentiation, 79-6406
Virus Replication, 79-6406
Testicular Neoplasms
Teratoid Tumor, 79-6406

Virus, Avian Erythroblastosis
RNA, Viral
Cell Transformation, Neoplastic
79-6384
Viral Proteins, 79-6384
Virus, Helper, 79-6384
Virus, Avian Sarcoma
Nucleic Acid Heteroduplexes, 79-6384

Virus, Avian Leukosis-Sarcoma
Antigenic Determinants
Genes, Viral, Review, 79-6074

Virus, Avian Sarcoma
Cell Transformation, Neoplastic
Chorioallantoic Membrane, 79-6381
Temperature Sensitive Mutants
79-6381

IgG
Phosphorylation, 79-6383
Phosphoproteins
Immunoprecipitation, 79-6382
Protein Kinase, 79-6382
Phosphotransferases, ATP
Antigen-Antibody Complex, 79-6383
Nucleotides, 79-6383
RNA, Messenger
Glycoproteins, 79-6380
Membrane Proteins, 79-6380
Polyribosomes, 79-6380
RNA, Viral
DNA Replication, 79-6379
Ribonuclease, 79-6379
Triton X 100, 79-6379
Viral Proteins
Cell Transformation, Neoplastic
79-6382
Protein Kinase, 79-6382
Virus, Avian Erythroblastosis
Nucleic Acid Heteroduplexes, 79-6384

Virus, Baboon C-Type RNA Tumor
Virus Replication
Chromosomes, Human, 6-12, 79-6421
Chromosomes, Human, 13-15, 79-6422
Chromosomes, Human, 19-20, 79-6422
Hybrid Cells, 79-6421, 79-6422

Virus, Bovine Papilloma
DNA, Viral
DNA-RNA Hybridization, 79-6420
Viral Proteins
Antibody Specificity, 79-6420
Warts
Isolation and Characterization
79-6420

Virus, C-Type RNA Tumor
Carcinogenic Activity
Hamster, Review, 79-6079
Lymphatic Diseases
Cross-Species Transmission, 79-6461
Isolation and Characterization, Turkey
79-6461
Sarcoma
Virus-Like Particles, 79-6502
Viral Proteins
Antigenic Determinants, 79-6460
Radioimmunoassay, 79-6460

Virus, Epstein-Barr
Burkitt's Lymphoma
Antibodies, Viral, 79-6524
Chromosome Aberrations, Review
79-6078
Epidemiology, Review, 79-6127
Cell Transformation, Neoplastic
Strain Difference, 79-6428
Chromosomes, Human, 13-15
Chromosome Aberrations, Review
79-6078
Cortisol Sodium Succinate
DNA Replication, 79-6432
Dexamethasone Sodium Phosphate
DNA Replication, 79-6432
DNA, Viral
Lymphocyte Transformation, 79-6430
Nucleic Acid Renaturation, 79-6430
B-Lymphocytes

Virus, Epstein-Barr (cont'd)
Chromosome Aberrations, Review
79-6078
Lymphocyte Transformation, Review
79-6078
Lymphosarcoma
Fetal Blood, 79-6429
Graft vs Host Reaction, 79-6429
Nasopharyngeal Neoplasms
Cell Line, 79-6428
Transplantation, Heterologous
79-6428
Peptides
Immunoprecipitation, 79-6431
12-O-Tetradecanoylphorbol-13-acetate
Antigens, Viral, 79-6431
Virus Activation, 79-6428
Uridine, 2'-Deoxy-5-iodo-
Virus Activation, 79-6428
Virus, Herpes Gorilla
Antigenic Determinants, 79-6424
DNA-DNA Hybridization, 79-6424

Virus, Feline Leukemia
Antigen-Antibody Reactions
Immune Response, 79-6419
Antigenic Determinants
Precancerous Conditions, 79-6419
Neutropenia
Lymphopenia, 79-6419
Precancerous Conditions, 79-6419
Virus Replication
Precancerous Conditions, 79-6419
Tissue Distribution, 79-6419

Virus, Friend Murine Leukemia
Erythroleukemia
Immunosuppression, 79-6408
12-O-Tetradecanoylphorbol-13-acetate
79-6278
Radiation, Ionizing
Immunosuppression, 79-6408
Strontium
Neoplasm Regression, Spontaneous
79-6408
Thymus Gland
Neoplasm Regression, Spontaneous
79-6408

Virus, Friend Spleen Focus-Forming
Antigens
Cell Membrane, 79-6407
Immunity, Cellular, 79-6407
Virus, Recombinant, 79-6407
Virus, Mink Cell Focus-Inducing
Antigenic Determinants, 79-6407

Virus, Gibbon Ape Lymphoma
RNA, Viral
Nucleotide Sequence, 79-6423
Virus, Woolly Monkey Sarcoma
Antigenic Determinants, 79-6423

Virus, Gross Murine Leukemia
Virus Replication
Age Factors, 79-6409
Tissue Distribution, 79-6409

Virus, Hamster Papova
DNA, Viral
Endonucleases, 79-6417
Isolation and Characterization
79-6417

Virus, Harvey Murine Leukemia
Virus, Kirsten Murine Leukemia
Nucleic Acid Heteroduplexes, 79-6415

Virus, Harvey Murine Sarcoma
Bacteriophages
DNA-DNA Hybridization, 79-6410
Nucleic Acid Heteroduplexes, 79-6410
DNA, Viral
Transformation, Genetic, 79-6410
Phosphoproteins
Cell Transformation, Neoplastic
79-6411
Immunoprecipitation, 79-6411
Virus, Kirsten Murine Sarcoma

Virus, Harvey Murine Sarcoma (cont'd)
Antigenic Determinants, 79-6411
Nucleic Acid Heteroduplexes, 79-6415

Virus, Helper

Virus, Abelson Murine Leukemia
Transformation Defective Mutants
79-6401
Viral Proteins, 79-6401
Virus, Avian Erythroblastosis
RNA, Viral, 79-6384
Virus, Murine Leukemia
Reverse Transcriptase, 79-6416
Virus, Murine Sarcoma
Ultraviolet Rays, 79-6392

Virus, Hepatitis

Australia Antigen
Epidemiology, Review, 79-6080
DNA Polymerase
Antigens, Viral, Review, 79-6080
Hepatitis
Australia Antigen, 79-6506
Epidemiology, Review, 79-6080
Histocompatibility Antigens, 79-6506
Liver Neoplasms
Epidemiology, Review, 79-6099

Virus, Herpes Gorilla

B-Lymphocytes
Cell Transformation, Neoplastic
79-6424
Virus, Epstein-Barr
Antigenic Determinants, 79-6424
DNA-DNA Hybridization, 79-6424

Virus, Herpes Salmiri

DNA, Viral
Cytosine, 5-Methyl-, 79-6425
Endonucleases, 79-6425
Lymphoma
DNA, Viral, 79-6425

Virus, Herpes Simplex 1

Antigens, Viral
Lymphocyte Transformation, 79-6426
Cervix Neoplasms
Lymphocyte Transformation, 79-6426
Cortisol
Virus Replication, 79-6427
Dwarfism
DNA Repair, 79-6377
Peptides
Cell Transformation, Neoplastic
79-6599
Ultraviolet Rays
Virus Reactivation, 79-6377
Virus Replication
Raji Cells, 79-6427

Virus, Herpes Simplex 2

Antigens, Viral
Lymphocyte Transformation, 79-6426
Brain Neoplasms
Encephalitis, 79-6532
Cervix Neoplasms
Carcinoma, Epidermoid, 79-6426
Lymphocyte Transformation, 79-6426
Cortisol
Virus Replication, 79-6427
Lung Neoplasms
Neoplasm Metastasis, 79-6532
Virus Replication
Raji Cells, 79-6427
Vulvar Neoplasms
Epidemiology, Review, 79-6125

Virus, Kirsten Murine Leukemia

Virus, Harvey Murine Leukemia
Nucleic Acid Heteroduplexes, 79-6415

Virus, Kirsten Murine Sarcoma

Phosphoproteins
Cell Transformation, Neoplastic
79-6411
Immunoprecipitation, 79-6411
Virus, Harvey Murine Sarcoma
Antigenic Determinants, 79-6411
Nucleic Acid Heteroduplexes, 79-6415

Virus, Kirsten Murine Sarcoma (cont'd)

Virus, Murine Leukemia
Pseudotype Formation, 79-6393
Virus, Murine Mammary Tumor
Pseudotype Formation, 79-6393
Virus, Rat C-Type RNA Tumor
Nucleic Acid Heteroduplexes, 79-6415
Virus, Rat Leukemia
Virus Replication, 79-6412

Virus-Like Particles

Glioblastoma Multiforme
Virus, RNA Tumor, 79-6459
T-Lymphocytes
Killer Cells, 79-6502
Oncogenic Viruses
Hamster, Review, 79-6079
Sarcoma
Virus, C-Type RNA Tumor, 79-6502
Virus, Polyoma
Cell-Free Assembly, 79-6437
DNA, Viral, 79-6437

Virus, LPV

Quinoline, 4-Nitro-, 1-Oxide
DNA Repair, 79-6227

Virus, Mengo

RNA, Viral
Ribonucleoproteins, 79-6464
Viral Proteins
Isolation and Characterization
79-6464
Virus Assembly, 79-6464

Virus, Mink Cell Focus-Inducing

Virus, Friend Spleen Focus-Forming
Antigenic Determinants, 79-6407

Virus, Moloney Murine Leukemia

Antigens
Cell Membrane, Review, 79-6077
Isolation and Characterization
79-6077
Lymphoma
Immunity, Cellular, 79-6486
Suppressor Cells, 79-6486
Virus, Abelson Murine Leukemia
Antigenic Determinants, 79-6403

Virus, Moloney Murine Sarcoma

DNA Restriction Enzyme
Cleavage Sites, 79-6413
DNA, Viral
Reverse Transcriptase, 79-6413

Virus, Moloney Murine Sarcoma-Leukemia

Reverse Transcriptase
Thermosensitivity, 79-6414
Virus Replication
Temperature Sensitive Mutants
79-6414

Virus, Murine Leukemia

Histocompatibility Antigens
Virus Replication, 79-6405
Leukemia, Lymphocytic
Radiation, Ionizing, 79-6366
T-Lymphocytes
Precancerous Conditions, Review
79-6083
Lymphoma
Genetics, 79-6405
Radiation, Ionizing
Precancerous Conditions, Review
79-6083
Reverse Transcriptase
Replication Defective Mutants
79-6416
Virus, Helper, 79-6416
Thymoma
Antigenic Determinants, 79-6083
Precancerous Conditions, Review
79-6083
Ultraviolet Rays
Virus Activation, 79-6392
Uridine, 5-Bromo-2'-deoxy-
Virus Activation, 79-6392
Uridine, 2'-Deoxy-5-iodo-

Virus, Murine Leukemia (cont'd)

Virus Activation, 79-6392
Virus, Kirsten Murine Sarcoma
Pseudotype Formation, 79-6393

Virus, Murine Mammary Tumor

A-Type Particles
DNA-DNA Hybridization, 79-6394
Adenocarcinoma
Antigens, Viral, 79-6396
Antigens, Viral
Lactation, 79-6396
Precancerous Conditions, 79-6396
Cell Transformation, Neoplastic
Virus Rescue, 79-6393
Dexamethasone
RNA, Viral, 79-6395
DNA, Viral
A-Type Particles, 79-6394
Hybrid Cells
DNA-DNA Hybridization, 79-6394
Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6396
Dexamethasone, 79-6395
DNA-DNA Hybridization, 79-6394
Genetics, 79-6398
Lactation, 79-6398
Viral Proteins
Radioimmunoassay, Milk, 79-6398
Virus, Kirsten Murine Sarcoma
Pseudotype Formation, 79-6393
Virus Replication
Epithelium, 79-6397
Host Range, 79-6393
Immunoperoxidase Assay, 79-6397

Virus, Murine Sarcoma

Lung Neoplasms
Neoplasm Metastasis, 79-6538
Protein Kinase
Acting, Binding, 79-6400
Antigen-Antibody Complex, 79-6400
Temperature Sensitive Mutant
79-6400
Sialic Acid
Cell Membrane, 79-6538
Neuraminidase, 79-6538
Sialoglycoproteins
Neoplasm Metastasis, 79-6538
Virus, Helper
Ultraviolet Rays, 79-6392

Virus, Papova

Carcinogenic Activity
Hamster, Review, 79-6079

Virus, Polyoma

Cell Transformation, Neoplastic
Cell Cycle Kinetics, 79-6435
Deletion Mutants, 79-6433
Temperature Sensitive Mutants
79-6435, 79-6438
DNA Restriction Enzyme
Antigens, Neoplasm, 79-6439
DNA, Viral
Cell Transformation, Neoplastic
79-6439
Deletion Mutants, 79-6433
Escherichia coli, 79-6434
Reentry Kinetics, 79-6436
Transformation, Genetic, 79-6434
Virus Replication, 79-6436
Extrachromosomal Inheritance
Carcinogenic Potential, 79-6434
Genes, Viral
Host Range Mutants, 79-6438
Temperature Sensitive Mutants
79-6438
Hyaluronidase
Cell Division, 79-6435
Peptides
Cell Transformation, Neoplastic
79-6599
Virus-Like Particles
Cell-Free Assembly, 79-6437
DNA, Viral, 79-6437

Virus, Radiation Leukemia
 Hematopoietic Stem Cells
 Virus Cultivation, 79-6399
Sarcoma, Reticulum Cell
 Histological Study, 79-6399
 Organ Specificity, 79-6399
 Thymus Neoplasms
 Lymphosarcoma, 79-6399

Virus, Rat C-Type RNA Tumor
 Virus, Kirsten Murine Sarcoma
 Nucleic Acid Heteroduplexes, 79-6415

Virus, Rat Leukemia
 Immune Serums
 Cell Transformation, Neoplastic
 79-6412
 Virus, Kirsten Murine Sarcoma
 Virus Replication, 79-6412

Virus, Rauscher Murine Leukemia
 Carcinogen, Chemical
 Focus Formation Assay, 79-6036
 Lymphoma
 Immunity, Passive, 79-6486
 RNA Polymerase
 Cell Transformation, Neoplastic
 79-6402
 Rifampicin, Dihydro-, 79-6402

Virus, Recombinant
 Virus, Friend Spleen Focus-Forming
 Antigens, 79-6407

Virus Replication
 Fibroma
 Virus, Vesicular Stomatitis, 79-6418
 Teratoid Tumor
 Virus, AKR Murine Leukemia
 79-6406
 Virus, SV40, 79-6450
 Virus, AKR Murine Leukemia
 Genetics, 79-6405
 Virus, Baboon C-Type RNA Tumor
 Chromosomes, Human, 6-12, 79-6421
 Chromosomes, Human, 13-15, 79-6422
 Chromosomes, Human, 19-20, 79-6422
 Hybrid Cells, 79-6421, 79-6422
 Virus, Feline Leukemia
 Precancerous Conditions, 79-6419
 Tissue Distribution, 79-6419
 Virus, Gross Murine Leukemia
 Age Factors, 79-6409
 Tissue Distribution, 79-6409
 Virus, Herpes Simplex 1
 Cortisol, 79-6427
 Raji Cells, 79-6427
 Virus, Herpes Simplex 2
 Cortisol, 79-6427
 Raji Cells, 79-6427
 Virus, Kirsten Murine Sarcoma
 Virus, Rat Leukemia, 79-6412
 Virus, Moloney Murine Sarcoma-
 Leukemia
 Temperature Sensitive Mutants
 79-6414
 Virus, Murine Leukemia
 Histocompatibility Antigens, 79-6405
 Virus, Murine Mammary Tumor
 Epithelium, 79-6397
 Host Range, 79-6393
 Immunoperoxidase Assay, 79-6397
 Virus, Polyoma
 DNA, Viral, 79-6436
 Virus, SV40
 Chromatin, 79-6444
 Virus, Vesicular Stomatitis
 Virus, Shope Rabbit Fibroma, 79-6418

Virus, RNA Tumor
 Glioblastoma Multiforme
 Reverse Transcriptase, 79-6459
 Virus-Like Particles, 79-6459
 Quinoline, 4-Nitro-, 1-Oxide
 DNA Repair, 79-6227

Virus, Rous-Associated
 Antigenic Determinants
 Virus, Recombinant, Review, 79-6074

Virus, Rous Sarcoma
 Antigenic Determinants
 Virus, Recombinant, Review, 79-6074

Antigens
 Antibody Specificity, 79-6388
 Cell Membrane, 79-6388
 Cell Transformation, Neoplastic
 79-6388
Antigens, Viral
 Cell Transformation, Neoplastic
 79-6386
 Cell Division
 Cations, Divalent, 79-6385
 Cell Transformation, Neoplastic
 Temperature Sensitive Mutants
 79-6387
 Chondroitin
 Cell Membrane, 79-6389
 Cell Transformation, Neoplastic
 79-6389
 Fetal Globulins
 Cell Transformation, Neoplastic
 79-6388
Fibroblasts
 Cell Transformation, Neoplastic
 79-6385
Genes, Viral
 Morphological Reversion, 79-6386
Glycoproteins
 Binding Sites, 79-6390
 Fibroblasts, 79-6390
Glycosaminoglycans
 Cell Transformation, Neoplastic
 79-6389
Growth Substances
 Cell Cycle Kinetics, 79-6387
 Temperature Sensitive Mutants
 79-6387
Histocompatibility Antigens
 Immunogenetics, 79-6498
 Transplantation Immunology, 79-6498
Hyaluronic Acid
 Cell Transformation, Neoplastic
 79-6389
T-Lymphocytes
 Immunogenetics, 79-6498
Neoplasms, Experimental
 Mouse, Nude, 79-6386
Sarcoma
 Immunogenetics, 79-6498

Virus, Sendai
 Leukemia L1210
 Immunization, 79-6479
 Transplantation Immunology, 79-6479
 Transplantation Immunology
 Temperature Sensitive Mutants
 79-6479

Virus, Shope Rabbit Fibroma
 Virus, Vesicular Stomatitis
 Carcinogenic Activity, 79-6418
 Virus Replication, 79-6418

Virus, Simian Sarcoma
 RNA, Viral
 Nucleotide Sequence, 79-6423

Virus, SV40
 Antigenic Determinants
 Antigen-Antibody Reactions, 79-6445
Antigens, Neoplasm
 Adenosine Triphosphatase, 79-6441
 Antigenic Determinants, Review
 79-6076
 Deletion Mutants, 79-6447
 DNA Replication, 79-6443
 Histocompatibility Antigens, 79-6076
 Immunoprecipitation, 79-6445
 Poly T, 79-6441
 Cell Transformation, Neoplastic
 Deletion Mutants, 79-6447
 Temperature Sensitive Mutants
 79-6447
Chromatin
 Acetylation, 79-6600
 Cleavage Sites, 79-6440
 DNA, Circular, 79-6440

Virus, SV40 (cont'd)
 DNA Restriction Enzyme, 79-6440
 79-6444
 Virus Replication, 79-6444
DNA, Bacterial
 Transformation, Genetic, 79-6442
DNA, Viral
 Chromosomes, 79-6444
 Microinjection Technique, 79-6443
Escherichia coli
 DNA-DNA Hybridization, 79-6442
Genes, Viral
 Deletion Mutants, 79-6438
 Temperature Sensitive Mutants
 79-6438
Histocompatibility Antigens
 Transplantation Immunology, 79-6448
Histones
 Acetylation, 79-6600
 Lymphocyte Transformation
 Concanavalin A, 79-6448
 Immune Serums, 79-6448
 Plant Agglutinins, 79-6448
T-Lymphocytes
 IgG, 79-6448
 Immunosuppression, 79-6448
Neoplasms, Experimental
 Histocompatibility Antigens, 79-6509
 Paraformaldehyde Fixation, 79-6509
 Phenylalanine, 4-Fluoro-
 Antigens, Neoplasm, 79-6446
 DNA Replication, 79-6446
RNA, Ribosomal
 Hybrid Cells, 79-6449
 Nucleolus Organizer Region, 79-6449
Sarcoma
 Fetal Globulins, Review, 79-6081
 Teratoid Tumor
 Antigens, Neoplasm, 79-6450
 Cell Differentiation, 79-6075
 Cell Line, Review, 79-6075
 RNA, Messenger, 79-6450
 Virus Replication, 79-6450
Ultraviolet Rays
 Cell Transformation, Neoplastic
 79-6356
 DNA Repair, 79-6356
 Xeroderma Pigmentosum
 Cell Transformation, Neoplastic
 79-6356
 DNA Repair, 79-6355

Virus, Vesicular Stomatitis
 Fibroma
 Virus Replication, 79-6418
 Virus, Shope Rabbit Fibroma
 Carcinogenic Activity, 79-6418
 Virus Replication, 79-6418

Virus, Woolly Monkey Sarcoma
 RNA, Viral
 Nucleotide Sequence, 79-6423
 Virus, Gibbon Ape Lymphoma
 Antigenic Determinants, 79-6423

Vulvar Neoplasms
 Carcinoma, Epidermoid
 Epidemiology, Review, 79-6125
 Precancerous Conditions
 Epidemiology, Review, 79-6125
 Virus, Herpes Simplex 2
 Epidemiology, Review, 79-6125

Warthin's Tumor
 see Adenolymphoma

Warts
 Virus, Bovine Papilloma
 Isolation and Characterization
 79-6420

Water Pollutants
 Chloroform Extracts
 Toxicity, Mouse, Rat, 79-6343
 79-6344
 Lymphosarcoma
 Chloroform Extracts, 79-6343
 79-6344
 Mammary Neoplasms, Experimental

Water Pollutants (cont'd)
Adenocarcinoma, 79-6343, 79-6344
Ovarian Neoplasms
Adenocarcinoma, 79-6343
Sarcoma
Chloroform Extracts, 79-6344
Thyroid Neoplasms
Chloroform Extracts, 79-6343

Water Pollution
Cadmium
Risk Factors, Review, 79-6109
Lead
Risk Factors, Review, 79-6109
Mercury
Risk Factors, Review, 79-6109
Polychlorobiphenyl Compounds
Risk Factors, Review, 79-6109
Polycyclic Hydrocarbons
Risk Factors, Review, 79-6109

Xeroderma Pigmentosum
Alkylating Agents
DNA Repair, 79-6067
Caffeine
DNA Repair, 79-6357

Xeroderma Pigmentosum (cont'd)
DNA Repair
Chromosome Aberrations, Review
79-6092
Complementation Group, 79-6355
79-6357
Isonicotinic Acid Hydrazide
DNA Repair, 79-6141
Manganese
DNA Repair, 79-6141
Radiation, Ionizing
DNA Repair, 79-6067
Skin Neoplasms
DNA Repair, Review, 79-6067
Ultraviolet Rays
DNA Repair, 79-6067, 79-6354
79-6355, 79-6356, 79-6357
Virus, SV40
Cell Transformation, Neoplastic
79-6356
DNA Repair, 79-6355

Yeasts
Cyclophosphamide
Mutation, 79-6191
Diethylamine, 2,2'-Dichloro-N-methyl-

Yeasts (cont'd)
Mutation, 79-6191
DNA Repair
Mutation, 79-6191
Formaldehyde
DNA Repair, 79-6163
Mutagenic Activity, 79-6163
Ultraviolet Rays
Mutation, 79-6191

Zearalenone
Food Contamination
Carcinogenic Potential, Review
79-6098

Zinc
Breast Neoplasms
Retinol, 79-6339
Occupational Hazard
Lung Neoplasms, 79-6054

Chemical Abstracts Service Registry Number Index

50-00-0, 79-6059, 79-6163
 50-02-2, 79-6395
 50-06-6, 79-6047, 79-6048, 79-6246
 79-6326, 79-6335
 50-07-7, 79-6224, 79-6226, 79-6273
 79-6365
 50-18-0, 79-6009, 79-6161, 79-6191
 79-6466, 79-6580
 50-21-5, 79-6187
 50-23-7, 79-6427
 50-28-2, 79-6030
 50-29-3, 79-6005, 79-6047, 79-6048
 79-6257
 50-31-7, 79-6098
 50-32-8, 79-6014, 79-6015, 79-6016
 79-6293, 79-6296, 79-6313, 79-6314
 79-6315, 79-6316, 79-6317, 79-6318
 79-6319, 79-6320, 79-6321, 79-6322
 79-6323, 79-6324, 79-6325, 79-6326
 79-6327, 79-6328, 79-6329, 79-6331
 79-6332, 79-6333, 79-6335, 79-6338
 50-67-9, 79-6539
 50-76-0, 79-6598
 50-81-7, 79-6245, 79-6289, 79-6333
 50-89-5, 79-6266
 50-91-9, 79-6365
 50-99-7, 79-6536
 51-12-7, 79-6141
 51-41-2, 79-6164, 79-6547
 51-48-9, 79-6595
 51-61-6, 79-6547
 51-75-2, 79-6191
 51-79-6, 79-6020, 79-6110, 79-6187
 79-6198
 52-90-4, 79-6007, 79-6149, 79-6199
 53-16-7, 79-6028
 53-70-3, 79-6015, 79-6296, 79-6313
 53-79-2, 79-6277
 53-86-1, 79-6272, 79-6274, 79-6277
 53-95-2, 79-6008, 79-6167, 79-6168
 79-6173
 53-96-3, 79-6139, 79-6166, 79-6167
 79-6169, 79-6170, 79-6172
 54-05-7, 79-6228, 79-6229
 54-11-5, 79-6322
 54-16-0, 79-6307
 54-36-4, 79-6313
 54-42-2, 79-6392, 79-6428
 54-85-3, 79-6141
 54-88-6, 79-6242
 54-92-2, 79-6141
 55-17-4, 79-6156
 55-18-5, 79-6110, 79-6112, 79-6184
 79-6190, 79-6192, 79-6193, 79-6194
 79-6195, 79-6197, 79-6205, 79-6209
 79-6288

55-80-1, 79-6236, 79-6237
 55-98-1, 79-6009
 56-23-5, 79-6147, 79-6149, 79-6207
 79-6259
 56-49-5, 79-6014, 79-6207, 79-6235
 79-6253, 79-6288, 79-6293, 79-6306
 79-6307, 79-6308, 79-6309, 79-6310
 79-6311, 79-6312, 79-6313, 79-6314
 79-6322, 79-6335, 79-6484, 79-6495
 79-6496, 79-6502, 79-6596
 56-53-1, 79-6021, 79-6024, 79-6025
 79-6048, 79-6104, 79-6125, 79-6341
 79-6342
 56-55-3, 79-6014, 79-6015, 79-6017
 79-6288, 79-6293, 79-6296, 79-6313
 56-57-5, 79-6224, 79-6227, 79-6358
 57-30-7, 79-6248
 57-63-6, 79-6350
 57-74-9, 79-6172, 79-6259
 57-83-0, 79-6345, 79-6346, 79-6347
 79-6349
 57-88-5, 79-6026, 79-6337
 57-97-6, 79-6014, 79-6078, 79-6276
 79-6289, 79-6290, 79-6291, 79-6292
 79-6293, 79-6294, 79-6295, 79-6297
 79-6298, 79-6299, 79-6300, 79-6301
 79-6302, 79-6309, 79-6313, 79-6314
 79-6317, 79-6327, 79-6345, 79-6346
 79-6363, 79-6497, 79-6516
 58-08-2, 79-6198, 79-6226, 79-6294
 79-6357, 79-6358
 58-22-0, 79-6307, 79-6351, 79-6352
 58-55-9, 79-6294
 58-89-9, 79-6259
 58-96-8, 79-6353
 59-14-3, 79-6225, 79-6226, 79-6273
 79-6392
 59-30-3, 79-6057
 59-89-2, 79-6165, 79-6180, 79-6182
 79-6215
 60-09-3, 79-6237, 79-6246, 79-6288
 60-11-7, 79-6005, 79-6247, 79-6310
 79-6507
 60-17-3, 79-6446
 60-24-2, 79-6471
 60-34-4, 79-6244
 60-56-0, 79-6150
 60-57-1, 79-6005, 79-6010, 79-6048
 79-6259
 60-92-4, 79-6164, 79-6231
 62-44-2, 79-6007, 79-6008
 62-49-7, 79-6194
 62-50-0, 79-6206, 79-6209, 79-6599
 62-68-0, 79-6150
 62-75-9, 79-6063, 79-6064, 79-6170
 79-6180, 79-6182, 79-6183, 79-6184
 79-6185, 79-6186, 79-6187, 79-6188
 79-6189, 79-6192, 79-6197, 79-6205
 79-6209, 79-6315

63-05-8, 79-6351
 63-42-3, 79-6593
 64-17-5, 79-6578
 65-23-6, 79-6565
 66-27-3, 79-6145, 79-6205, 79-6209
 79-6466
 66-81-9, 79-6159, 79-6277, 79-6598
 67-21-0, 79-6156
 67-42-5, 79-6164
 67-56-1, 79-6147
 67-63-0, 79-6147
 67-66-3, 79-6259
 67-68-5, 79-6205, 79-6209
 68-22-4, 79-6348
 68-26-8, 79-6019, 79-6026, 79-6339
 68-96-2, 79-6352
 69-05-6, 79-6145
 69-72-7, 79-6550
 70-18-8, 79-6007, 79-6149, 79-6150
 79-6199, 79-6219, 79-6323
 70-25-7, 79-6218, 79-6219, 79-6220
 79-6221, 79-6222, 79-6223, 79-6224
 79-6466
 71-43-2, 79-6004, 79-6238
 72-33-3, 79-6350
 72-55-9, 79-6048
 72-57-1, 79-6488
 73-40-5, 79-6324
 74-55-5, 79-6057
 74-79-3, 79-6224, 79-6457, 79-6592
 75-01-4, 79-6104, 79-6113, 79-6151
 79-6165
 75-21-8, 79-6049
 75-35-4, 79-6151
 75-44-5, 79-6149
 76-44-8, 79-6259
 79-01-6, 79-6151, 79-6207
 79-36-7, 79-6151
 79-44-7, 79-6113
 81-07-2, 79-6060, 79-6061, 79-6252
 79-6253, 79-6578
 81-88-9, 79-6264
 82-28-0, 79-6262
 83-44-3, 79-6051
 83-72-7, 79-6261
 83-89-6, 79-6145
 84-17-3, 79-6024
 85-01-8, 79-6304
 86-54-4, 79-6254
 90-45-9, 79-6265
 90-65-3, 79-6257
 91-59-8, 79-6011

91-64-5, 79-6066
 92-62-6, 79-6265, 79-6287
 92-67-1, 79-6241
 92-71-7, 79-6313
 92-87-5, 79-6011, 79-6260
 94-59-7, 79-6020
 95-53-4, 79-6241
 95-80-7, 79-6240
 95-95-4, 79-6012
 96-09-3, 79-6157, 79-6248
 97-00-7, 79-6298
 97-56-3, 79-6234
 97-77-8, 79-6148
 99-56-9, 79-6213
 100-42-5, 79-6248
 100-61-8, 79-6245
 103-69-5, 79-6241
 103-90-2, 79-6007
 106-49-0, 79-6241
 106-50-3, 79-6237
 106-88-7, 79-6157
 106-93-4, 79-6046, 79-6150
 107-06-2, 79-6046, 79-6150, 79-6151
 107-13-1, 79-6181
 107-22-2, 79-6160
 107-92-6, 79-6599
 108-44-1, 79-6241
 108-45-2, 79-6213
 110-60-1, 79-6275
 110-91-8, 79-6057, 79-6180
 112-63-0, 79-6179
 115-02-6, 79-6508
 117-79-3, 79-6262
 117-81-7, 79-6006
 117-82-8, 79-6006
 117-83-9, 79-6006
 117-89-5, 79-6164
 118-71-8, 79-6160
 118-74-1, 79-6005
 119-93-7, 79-6260
 121-69-7, 79-6241
 122-39-4, 79-6245
 125-04-2, 79-6432
 126-72-7, 79-6046
 126-99-8, 79-6050, 79-6158
 127-07-1, 79-6186
 127-18-4, 79-6151
 127-47-9, 79-6200
 128-37-0, 79-6110
 129-15-7, 79-6262
 131-48-6, 79-6538
 132-64-9, 79-6249

133-06-2, 79-6157
 134-32-7, 79-6241
 137-26-8, 79-6199
 138-41-0, 79-6253
 139-13-9, 79-6107
 141-05-9, 79-6219, 79-6322
 143-50-0, 79-6005, 79-6259
 143-67-9, 79-6593
 144-90-1, 79-6598
 148-24-3, 79-6055
 148-82-3, 79-6009
 149-29-1, 79-6257
 150-90-3, 79-6536
 153-78-6, 79-6157, 79-6167, 79-6169
 79-6178, 79-6235
 154-93-8, 79-6211
 156-59-2, 79-6151
 189-55-9, 79-6169
 189-64-0, 79-6330
 189-66-2, 79-6330
 192-97-2, 79-6332
 198-55-0, 79-6326
 206-44-0, 79-6326
 218-01-9, 79-6015, 79-6304, 79-6313
 244-63-3, 79-6016
 260-94-6, 79-6013
 262-12-4, 79-6249
 288-13-1, 79-6148
 298-81-7, 79-6071, 79-6287, 79-6359
 299-42-3, 79-6057
 299-84-3, 79-6012
 302-01-2, 79-6023, 79-6141
 302-33-0, 79-6313
 302-79-4, 79-6277
 304-28-9, 79-6171
 309-00-2, 79-6010, 79-6259
 362-74-3, 79-6275
 363-49-5, 79-6167
 427-51-0, 79-6352
 431-03-8, 79-6160
 434-13-9, 79-6162
 443-48-1, 79-6055, 79-6216, 79-6217
 446-86-6, 79-6009, 79-6255
 463-56-9, 79-6057
 474-25-9, 79-6208
 479-61-8, 79-6131
 486-84-0, 79-6016
 494-38-2, 79-6265
 501-30-4, 79-6160
 505-60-2, 79-6053, 79-6104
 506-32-1, 79-6272, 79-6277, 79-6278
 518-47-8, 79-6263
 518-75-2, 79-6256

519-62-0, 79-6131
 522-40-7, 79-6239
 530-78-9, 79-6274
 533-67-5, 79-6311
 540-59-0, 79-6151
 540-73-8, 79-6174, 79-6175, 79-6176
 79-6177
 542-88-1, 79-6012, 79-6113
 553-24-2, 79-6287
 554-01-8, 79-6425
 556-10-5, 79-6202
 568-70-7, 79-6289, 79-6290
 568-75-2, 79-6289, 79-6290
 569-61-9, 79-6242
 578-76-7, 79-6170, 79-6186, 79-6315
 586-17-4, 79-6164, 79-6547
 590-96-5, 79-6146
 592-62-1, 79-6146, 79-6148
 595-33-5, 79-6350
 601-34-3, 79-6338
 604-59-1, 79-6166, 79-6291, 79-6313
 79-6322, 79-6341
 607-57-8, 79-6288
 610-49-1, 79-6169
 613-13-8, 79-6169, 79-6178
 615-05-4, 79-6167, 79-6235
 615-53-2, 79-6207
 621-90-9, 79-6237, 79-6246
 627-22-5, 79-6158
 628-87-5, 79-6245
 630-08-0, 79-6105
 637-07-0, 79-6153, 79-6154, 79-6155
 79-6171
 671-16-9, 79-6243, 79-6244, 79-6299
 683-51-2, 79-6056
 684-93-5, 79-6065, 79-6148, 79-6203
 79-6204, 79-6205, 79-6206, 79-6208
 79-6209, 79-6346, 79-6466
 759-73-9, 79-6205, 79-6206, 79-6209
 79-6210
 764-41-0, 79-6158
 797-63-7, 79-6352
 838-95-9, 79-6024, 79-6302, 79-6340
 869-01-2, 79-6206
 892-17-1, 79-6303
 908-35-0, 79-6313
 926-06-7, 79-6209
 930-55-2, 79-6212, 79-6315
 931-17-9, 79-6160
 937-40-6, 79-6197, 79-6233
 989-38-8, 79-6264
 1116-54-7, 79-6062
 1145-73-9, 79-6024, 79-6302, 79-6340
 1162-65-8, 79-6019, 79-6020, 79-6021
 79-6279, 79-6280, 79-6281

1199-18-4, 79-6307
 1239-45-8, 79-6152
 1332-21-4, 79-6052, 79-6053, 79-6054
 79-6055, 79-6102, 79-6104, 79-6105
 79-6115, 79-6123, 79-6133, 79-6231
 79-6570
 1332-82-7, 79-6219
 1385-95-1, 79-6281
 1439-07-2, 79-6316
 1746-01-6, 79-6012, 79-6249, 79-6250
 79-6313, 79-6327
 1910-36-7, 79-6246
 1910-42-5, 79-6187
 2058-67-5, 79-6246
 2235-59-8, 79-6244
 2246-44-8, 79-6241
 2303-16-4, 79-6056
 2303-17-5, 79-6056
 2385-85-5, 79-6005
 2392-39-4, 79-6432
 2498-66-0, 79-6290
 2530-37-2, 79-6257
 2541-69-7, 79-6014, 79-6293
 3083-23-6, 79-6157, 79-6248, 79-6322
 3308-64-3, 79-6308, 79-6312
 3343-08-6, 79-6308
 3343-12-2, 79-6312
 3583-47-9, 79-6158
 3688-53-7, 79-6046
 4213-45-0, 79-6145
 4463-22-3, 79-6173
 4940-11-8, 79-6160
 5307-14-2, 79-6213
 6051-87-2, 79-6313
 6098-46-0, 79-6246
 6219-67-6, 79-6213
 6795-23-9, 79-6280
 7227-91-0, 79-6165
 7390-95-6, 79-6312
 7439-89-6, 79-6054, 79-6141
 7439-92-1, 79-6054, 79-6109
 7439-95-4, 79-6385
 7439-96-5, 79-6140, 79-6141
 7439-97-6, 79-6107, 79-6109
 7440-02-0, 79-6053, 79-6054, 79-6105
 7440-21-3, 79-6102
 7440-23-5, 79-6598
 7440-38-2, 79-6053, 79-6115
 7440-41-7, 79-6054, 79-6105, 79-6134
 7440-43-9, 79-6109
 7440-44-0, 79-6097, 79-6585
 7440-47-3, 79-6054, 79-6105, 79-6136
 7440-50-8, 79-6054, 79-6140, 79-6141
 7440-57-5, 79-6585

7440-61-1, 79-6371
 7440-65-5, 79-6054, 79-6339
 7440-66-6, 79-6054, 79-6339
 7440-70-2, 79-6164, 79-6385
 7632-00-0, 79-6061, 79-6179, 79-6180
 7646-79-9, 79-6219
 7681-49-4, 79-6593
 7697-37-2, 79-6101, 79-6109, 79-6110
 7720-78-7, 79-6289, 79-6333
 7738-94-5, 79-6115
 7771-44-0, 79-6272, 79-6277, 79-6278
 7778-50-9, 79-6136, 79-6138
 7782-77-6, 79-6060, 79-6110, 79-6232
 79-6245
 7789-00-6, 79-6137, 79-6138
 8001-30-7, 79-6279
 8001-35-2, 79-6002, 79-6003
 8001-58-9, 79-6053, 79-6097
 8002-05-9, 79-6130
 8003-34-7, 79-6047
 8006-61-9, 79-6207
 8007-45-2, 79-6053, 79-6097
 8008-60-4, 79-6565, 79-6581
 8012-95-1, 79-6238
 8049-97-6, 79-6268
 8063-94-3, 79-6102, 79-6105
 9000-69-5, 79-6176
 9000-71-9, 79-6492
 9001-05-2, 79-6140
 9001-45-0, 79-6176, 79-6201, 79-6325
 9001-54-1, 79-6435
 9001-63-2, 79-6480
 9001-77-8, 79-6201, 79-6482, 79-6525
 9001-78-9, 79-6095, 79-6280
 9002-62-4, 79-6027, 79-6029, 79-6352
 9002-72-6, 79-6352
 9002-76-0, 79-6539
 9002-86-2, 79-6102, 79-6105
 9002-93-1, 79-6379
 9003-98-9, 79-6177
 9004-54-0, 79-6229, 79-6490
 9004-61-9, 79-6389
 9006-04-6, 79-6238
 9008-11-1, 79-6463
 9008-22-4, 79-6478
 9013-80-3, 79-6229, 79-6490
 9015-73-0, 79-6265
 9035-50-1, 79-6151, 79-6166, 79-6318
 9037-22-3, 79-6176
 9038-36-2, 79-6539
 9044-66-0, 79-6229, 79-6490
 10025-73-7, 79-6136
 10028-17-8, 79-6266, 79-6353

10033-99-5, 79-6158
 10043-92-2, 79-6371
 10088-79-6, 79-6257
 10108-64-2, 79-6135
 10124-50-2, 79-6132
 10588-01-9, 79-6157
 11006-34-1, 79-6131
 11028-71-0, 79-6296, 79-6448, 79-6465
 79-6516
 11097-69-1, 79-6305, 79-6326, 79-6335
 11104-36-2, 79-6229, 79-6490
 11121-03-2, 79-6229, 79-6490
 12001-28-4, 79-6052, 79-6053, 79-6054
 79-6055, 79-6102, 79-6104, 79-6105
 79-6115, 79-6123, 79-6133, 79-6231
 79-6570
 12001-29-5, 79-6052, 79-6053, 79-6054
 79-6055, 79-6102, 79-6104, 79-6105
 79-6115, 79-6123, 79-6133, 79-6231
 79-6570
 12035-72-2, 79-6142, 79-6499
 12172-73-5, 79-6052, 79-6053, 79-6054
 79-6055, 79-6102, 79-6104, 79-6105
 79-6115, 79-6123, 79-6133, 79-6231
 79-6570
 12587-46-1, 79-6070, 79-6372
 12626-85-6, 79-6229, 79-6490
 13073-35-3, 79-6156
 13255-50-0, 79-6244
 13256-07-0, 79-6214
 13345-61-4, 79-6290
 13463-39-3, 79-6054
 13967-73-2, 79-6408
 13981-16-3, 79-6372, 79-6373, 79-6374
 14301-11-2, 79-6024, 79-6302, 79-6340
 14596-10-2, 79-6375
 14807-96-6, 79-6055
 14901-08-7, 79-6146
 14930-96-2, 79-6195, 79-6593
 15611-43-5, 79-6131
 15663-27-1, 79-6143
 16339-07-4, 79-6165
 16503-25-6, 79-6158
 16561-29-8, 79-6268, 79-6269, 79-6270
 79-6271, 79-6272, 79-6273, 79-6274
 79-6275, 79-6276, 79-6277, 79-6278
 79-6308, 79-6309, 79-6361, 79-6428
 79-6431
 16566-62-4, 79-6330
 16812-54-7, 79-6142, 79-6499
 17068-78-9, 79-6052, 79-6053, 79-6054
 79-6055, 79-6102, 79-6104, 79-6105
 79-6115, 79-6123, 79-6133, 79-6231
 79-6570
 17513-40-5, 79-6290
 17573-29-4, 79-6332
 17673-25-5, 79-6189, 79-6266, 79-6274
 79-6299
 17924-92-4, 79-6098

19253-88-4, 79-6059
 19477-24-8, 79-6338
 19750-45-9, 79-6149
 20307-32-8, 79-6338
 20535-83-5, 79-6065, 79-6170, 79-6186
 79-6315
 21884-44-6, 79-6257
 22204-53-1, 79-6274
 23537-16-8, 79-6257
 24909-09-9, 79-6328, 79-6331, 79-6332
 79-6333
 24928-15-2, 79-6274
 24928-17-4, 79-6268, 79-6274, 79-6277
 24961-39-5, 79-6319, 79-6336
 24967-93-9, 79-6389
 25013-16-5, 79-6187, 79-6291, 79-6301
 25090-77-1, 79-6189
 25104-18-1, 79-6317
 25405-85-0, 79-6274, 79-6275, 79-6277
 25843-45-2, 79-6204, 79-6378
 26241-63-4, 79-6189, 79-6266, 79-6274
 79-6299
 26317-27-1, 79-6131
 26550-68-5, 79-6338

26628-22-8, 79-6144, 79-6157, 79-6593
 27100-68-1, 79-6478
 27208-37-3, 79-6326
 28302-36-5, 79-6131
 28622-84-6, 79-6332, 79-6333
 32215-02-4, 79-6280
 32627-52-4, 79-6131
 34669-57-3, 79-6162
 34807-41-5, 79-6268, 79-6272, 79-6277
 37224-17-2, 79-6229, 79-6490
 37337-52-3, 79-6265
 37574-47-3, 79-6017, 79-6316, 79-6319
 79-6334, 79-6336
 37691-11-5, 79-6361
 39834-38-3, 79-6309
 41286-73-1, 79-6232
 41593-31-1, 79-6304
 51773-92-3, 79-6228
 54687-66-0, 79-6254
 56484-47-0, 79-6328, 79-6331, 79-6332
 79-6333
 56856-83-8, 79-6148, 79-6165
 57303-99-8, 79-6017, 79-6315, 79-6328
 79-6332, 79-6333

58130-93-1, 79-6021
 59957-91-4, 79-6315
 59963-01-8, 79-6017, 79-6319, 79-6327
 79-6329, 79-6335, 79-6336
 60454-72-0, 79-6229, 79-6490
 60784-46-5, 79-6211
 61258-11-5, 79-6402
 61413-38-5, 79-6305
 61695-74-7, 79-6336
 64977-44-2, 79-6305
 64977-45-3, 79-6305
 64977-46-4, 79-6305
 64977-47-5, 79-6305
 64977-48-6, 79-6305
 64977-49-7, 79-6305
 66944-56-7, 79-6244
 66997-69-1, 79-6304
 67694-87-5, 79-6304
 67823-52-3, 79-6139

Wiswesser Line Notation Index

..H2.CR-O4, 79-6115
 .AM, 79-6375
 .AS, 79-6053, 79-6115
 .AU, 79-6585
 .BE, 79-6054, 79-6105, 79-6134
 .C, 79-6097, 79-6585
 .CA, 79-6164, 79-6385
 .CD 79-6109
 .CD.. G2, 79-6135
 .CO..G2, 79-6219
 .CR 79-6054, 79-6105, 79-6136
 .CR..G3, 79-6136
 .CU 79-6054, 79-6140, 79-6141
 .FE, 79-6054, 79-6141
 .FE..S-O4, 79-6289, 79-6333
 .HG, 79-6107, 79-6109
 .KA..AS2-O3-Q, 79-6132
 .KA2.CR-O2-Q2, 79-6137, 79-6138
 .KA2.CR2-O5-Q2, 79-6136, 79-6138
 .MG, 79-6385
 .MN, 79-6140, 79-6141
 .NA, 79-6598
 .NA..F, 79-6593
 .NA..N-O-Q, 79-6061, 79-6179, 79-6180
 .NA2.CR2-O5-Q2, 79-6157
 .NI, 79-6053, 79-6054, 79-6105
 .NI3.S2, 79-6142, 79-6499
 .PB, 79-6054, 79-6109
 .PU 79-6273, 79-6372, 79-6374
 .RN, 79-6371
 .SI, 79-6102
 .SR, 79-6408
 .UR, 79-6371
 .ZN, 79-6054, 79-6339
 C O, 79-6105
 EIYE1O 3PO, 79-6046
 E2E, 79-6046, 79-6150
 G 6-R, 79-6005
 GR BR DG EOPS&O1&O1, 79-6012
 GR DOXVO2&1&1, 79-6153, 79-6154
 79-6155, 79-6171
 GVG, 79-6149
 GVN1&1, 79-6113
 GXGGG, 79-6147, 79-6149, 79-6207
 79-6259
 GXGGYR DG&R DG, 79-6005, 79-6047
 79-6048, 79-6257
 GYGG, 79-6259
 GYGUYG, 79-6151
 GYGUYGISVNY1&1&Y1&1, 79-6056
 GYGUYR DG&R DG, 79-6048

GYGU1, 79-6151
 GYGU1G, 79-6151, 79-6207
 GYGVG, 79-6151
 G1O1G, 79-6012, 79-6113
 G1UYGISVNY1&1&Y1&1, 79-6056
 G1U1, 79-6104, 79-6113, 79-6151, 79-6165
 G1U1G, 79-6151
 G2G, 79-6046, 79-6150
 G2N1&2G, 79-6191
 G2S2G, 79-6053, 79-6104
 G2U2G, 79-6158
 L B656 HHJ KNUNUN KNUNUN
 79-6139
 L B656 HHJ EMV1, 79-6139, 79-6166
 79-6167, 79-6169, 79-6170, 79-6172
 L B656 HHJ EMV1 KMV1, 79-6171
 L B656 HHJ EMV1 KQ, 79-6167
 L B656 HHJ ENQV1, 79-6008, 79-6167
 79-6168, 79-6173
 L B656 HHJ ENUNUN KNUNUN
 79-6139
 L B656 HHJ ENW, 79-6288
 L B656 HHJ KNUNUN, 79-6139
 L B656J HHJ EZ, 79-6157, 79-6167
 79-6169, 79-6178, 79-6235
 L B666J, 79-6304
 L C555 A DU IUTJ AG AG BG FG HG
 IG JG, 79-6259
 L C555 A IUTJ AG AG BG DG EG HG
 IG JG, 79-6172, 79-6259
 L C6566 1A PJ, 79-6326
 L C666 BV IVJ DNW E1, 79-6262
 L C666 BV IVJ DZ E1, 79-6262
 L C666 BV IVJ EZ, 79-6262
 L C666J DZ, 79-6169
 L C666J EZ, 79-6169, 79-6178
 L D5 C555 A D- EU JUTJ AG AG BG IG
 JG KG, 79-6010, 79-6259
 L D6 B66 O666 JN UN&T&T&T&J
 79-6330
 L D6 B66 O666J, 79-6330
 L D6 B666 T&T&T&J C1 J1 LQ MQ
 79-6309
 L D6 B666J, 79-6014, 79-6015, 79-6017
 79-6288, 79-6293, 79-6296, 79-6313
 L D6 B666J CVH J1, 79-6290
 L D6 B666J C1 JVH, 79-6290
 L D6 B666J C1 J1, 79-6014, 79-6078
 79-6276, 79-6289, 79-6290, 79-6291
 79-6292, 79-6293, 79-6294, 79-6295
 79-6297, 79-6298, 79-6299, 79-6300
 79-6301, 79-6302, 79-6309, 79-6313
 79-6314, 79-6317, 79-6327, 79-6345
 79-6346, 79-6363, 79-6497, 79-6516
 L D6 B666J C1 J1Q, 79-6289, 79-6290
 L D6 B666J C1Q J1, 79-6289, 79-6290

L D6 B666J J, 79-6014, 79-6293
 L D6 B666J J1E, 79-6319, 79-6336
 L D6 B6666 2AB TJ, 79-6014, 79-6015
 79-6016, 79-6293, 79-6296, 79-6313
 79-6314, 79-6315, 79-6316, 79-6317
 79-6318, 79-6319, 79-6320, 79-6321
 79-6322, 79-6323, 79-6324, 79-6325
 79-6326, 79-6327, 79-6328, 79-6329
 79-6331, 79-6332, 79-6333, 79-6335
 79-6338
 L D6 B6666 2AB TJ FQ, 79-6332
 L D6 B6666 2AB TJ FQ EQ, 79-6328
 79-6331, 79-6332, 79-6333
 L D6 B6666 2AB TJ GQ HQ, 79-6017
 79-6315, 79-6328, 79-6332, 79-6333
 L D6 B6666 2AB TJ LQ MQ, 79-6332
 79-6333
 L D6666 B6 2AB TJ, 79-6332
 L E3 B675 MV IU NUTJ BQ C1 DQ EQ
 F1 F1 J1Q LQ N1
 79-6189, 79-6266, 79-6274, 79-6299
 L E5 B666 FV OV MUTJ A1 E1, 79-6351
 L E5 B666 FVTTT&J E1 OQ, 79-6028
 L E5 B666 LUTJ A1 E1 FY&3Y QQ -
 B&AEFO, 79-6026, 79-6337
 L E5 B666 OV AHTTT&J A1 CQ E1
 FV1Q FQ G1 -A&B -B&ACEFG
 79-6395
 L E5 B666 OV MUTJ A1 CQ E1 FV1Q
 FQ -B&ACEF, 79-6427
 L E5 B666 OV MUTJ A1 E1 FQ -B&AEF
 79-6307, 79-6351, 79-6352
 L E5 B666 OV MUTJ A1 E1 FV1 -
 B&AEF, 79-6345, 79-6346, 79-6347
 79-6349
 L E5 B666 OV MUTJ A1 E1 FV1 FQ -
 A&L -B&AEF, 79-6352
 L E5 B666TJ A1 DQ E1 FY1&2VQ HQ
 79-6208
 L E5 B666TJ A1 DQ E1 FY1&2VQ OQ
 79-6051
 L E5 B666TJ A1 E1 FY1&2VQ OQ -
 B&AEFMO, 79-6162
 L E5 B666TTT&J E1 FQ FIUUI OQ
 79-6350
 L E5 B666TTT&J E1 FQ OQ, 79-6030
 L E6 B666J, 79-6015, 79-6304, 79-6313
 L E6 B666J CF L1, 79-6305
 L E6 B666J DF L1, 79-6305
 L E6 B666J FF L1, 79-6305
 L E6 B666J HF L1, 79-6305
 L E6 B666J L1 MF, 79-6305
 L E6 B666J L1 OF, 79-6305
 L E6 B666J L1 QF, 79-6305
 L E6 D6656 1A T PV OHJ R, 79-6308
 L E6 D6656 1A T&T&T&T&J JQ KQ OQ
 R1, 79-6308
 L E6 D6656 1A T&T&T&T&J PQ R1
 79-6308, 79-6312

L E6 D6656 1A T&&T&J R1, 79-6014
79-6207, 79-6235, 79-6253, 79-6288
79-6293, 79-6306, 79-6307, 79-6308
79-6309, 79-6310, 79-6311, 79-6312
79-6313, 79-6314, 79-6322, 79-6335
79-6484, 79-6495, 79-6496, 79-6502
79-6596

L E6 D6656 1A T&&T&TJ R1 SQ TQ
79-6312

L E6 D6656 1A T&T&T&J KQ LQ R1
79-6312

L E6 D6656 1A TT&&T&J HQ IQ R1
79-6309, 79-6312

L F5 C6 B663 PV LU NUTJ B1 F1 GV1
MG-B&BFGM, 79-6352

L G6 D6 B666J, 79-6015, 79-6296
79-6313

L545 B4 C5 D 4ABCE J DVTJ-/G 10
79-6005, 79-6259

L545 B4 C5 D 4ABCE J TJ-/G 12
79-6005

L6TJ AG BG CG DG EG FG *GAMMA
79-6259

L6UTJ A1 A1 B1U1Y1&U2U1Y1VQ&1
C1 -T, 79-6277

L6UTJ A1 BL/U1Y1&U2/ 2Q C1 C1 -T
79-6019, 79-6026, 79-6339

L6VVTJ, 79-6160

L64TJ A1 B1U1Y&U2U1Y&U2OV1 C1
C1, 79-6200

L66 BV EVJ CQ, 79-6261

L66J BZ, 79-6241

L66J BZ C1, 79-6241

L66J CZ, 79-6011

NC1U1, 79-6181

OC 4-NI-, 79-6054

ONMVM3, 79-6206

ONN1&VO2, 79-6207

ONN1&1, 79-6063, 79-6064, 79-6170
79-6180, 79-6182, 79-6183, 79-6184
79-6185, 79-6186, 79-6187, 79-6188
79-6189, 79-6192, 79-6197, 79-6205
79-6209, 79-6315

ONN1&1OV1, 79-6148, 79-6165

ONN1&1R, 79-6197, 79-6233

ONN1YQ1&1V1, 79-6196

ONN2&2, 79-6110, 79-6112, 79-6184
79-6190, 79-6192, 79-6193, 79-6194
79-6195, 79-6197, 79-6205, 79-6209
79-6288

ONN2GVM2G, 79-6211

ONN2Q&2Q, 79-6062

ONN2Y1&1&YV1&1, 79-6197

ONN5&1, 79-6214

ON1&UN1, 79-6204, 79-6378

ON1&UN1OV1, 79-6146, 79-6148

OS1&1, 79-6205, 79-6209

QR BG DG EG, 79-6012

QR DMV1, 79-6007

QR DYU2&YU2&R DQ, 79-6024

QR DY2& 2U, 79-6021, 79-6024, 79-6025
79-6048, 79-6104, 79-6125, 79-6341
79-6342

QVR BG CG FG, 79-6098

QVR BQ, 79-6550

QVYQYQVQ & 2 &621 T6NJ C1 2/XV/
&622, 79-6313

QVYZ1OV1UNN &10/11, 79-6508

QVYZ1R DN2G2G -L, 79-6009

QVYZ2S2 -DL, 79-6156

QV1 3N, 79-6107

QV1N1VQ2O 22, 79-6164

QV1UYO1&VYU1&1, 79-6257

QV3, 79-6599

QV4U3U3U3U6, 79-6272, 79-6277
79-6278

QYR&YM1, 79-6057

QYVQ, 79-6187

QY1&1, 79-6147

Q1, 79-6147

QINUNO&1, 79-6146

Q1YGU1, 79-6056

Q2, 79-6578

Q2K &Q, 79-6194

Q2MVNNO&2G, 79-6211

R, 79-6004, 79-6238

RMR, 79-6245

RVON1&R DNUNR, 79-6246

SHCN, 79-6057

SH1YVQZ, 79-6007, 79-6149, 79-6199

SH2Q, 79-6471

T B656 EN HMJ FT B656 EN HMJ F1
79-6016

T B656 HOJ, 79-6249

T B656 IN JN LN MNJ K1Q, 79-6254

T B666 HKJ EZ H2 IR& LZ &E &9/26
79-6152

T C566 DO LVOJ BO1, 79-6071, 79-6287
79-6359

T C666 BN INJ E1 FZ LN1&1 &GH
79-6287

T C666 BNJ, 79-6013

T C666 BNJ EG IMY&3N2&2 LO1
79-6145

T C666 BNJ EG IM2N2G2G LO1 &GH
&GH &QH, 79-6145

T C666 BNJ EN1&1 MN1&1, 79-6265

T C666 BNJ EZ MZ, 79-6265, 79-6287

T C666 BNJ IZ, 79-6265

T C666 BO EV INJ D1 FZ N1 G- K-/
VM- OT5-16- AN FVN IVN LVO PVM
SVTJ G1 J1 KY N1 RY2, 79-6598

T C666 BO EVJ TR BVQ& MO &-NA- 2
79-6263

T C666 BOJ EN2&2 IR BVQ& MN2&2
&G, 79-6264

T DB B556 BN EM JV MVTTT&J GO1
H1OVZ KZ L1, 79-6224, 79-6226
79-6273, 79-6365

T D36 I666 B6 2AB U EOT&&&&J
79-6017, 79-6316, 79-6319, 79-6334
79-6336

T D6 B66 O666 EN PNT&&T&J
79-6330

T E3 D5 C555 A D- FO KUTJ AG AG BG
JG KG LG, 79-6005, 79-6010, 79-6048
79-6259

T E3 D6 B6666 2AB U FOTT&&&&J HQ
IQ 79-6017, 79-6319, 79-6327, 79-6329
79-6335, 79-6336

T F5 C6 B655 DOV GV OO QO
RUT&&TTJ LO1, 79-6019, 79-6020
79-6021, 79-6279, 79-6280, 79-6281

T3OTJ, 79-6049

T3OTJ BR, 79-6157, 79-6248

T3OTJ BXGGG, 79-6157, 79-6248
79-6322

T3OTJ B1G C1G, 79-6158

T3OTJ B2, 79-6157

T3STJ B2UUN, 79-6021

T5MVSTJ DVQ, 79-6149

T5N CNJ A1 BSH, 79-6150

T5N CNJ A2Q B1 ENW, 79-6055
79-6216, 79-6217

T5N COJ BR& DR, 79-6313

T5NTJ ANO, 79-6212, 79-6315

T5OJ BYVZU1- BT5OJ ENW, 79-6046

T5OV EHV CQ DQ EYQ1Q, 79-6245
79-6289, 79-6333

T56 BM DN FMYMVJ GUM, 79-6324

T56 BM DN FNVNVJ F1 H1, 79-6294

T56 BMJ D2Z GQ, 79-6539

T56 BN DN FMYMVJ B1 GUM, 79-6170
79-6186, 79-6315

T56 BN DN FN HNJ INNO&1 D-
BT5OTJ CQ DQ EIQ -A&CD
79-6232

T56 BN DN FN HNJ IN1&1 D- BT5OTJ
CQ DMVYZ1R DO1& EIQ
79-6277

T56 BN DN FNVNVJ B1 F1 H1, 79-6198
79-6226, 79-6294, 79-6357, 79-6358

T56 BNJ BVR DG& C1 D1VQ GO1
79-6272, 79-6274, 79-6277

T56 BNJ D1VQ GQ, 79-6307

T56 BO DO CHJ G2U1, 79-6020

T56 BOV GO IU&TJ FQ, 79-6257

T56 BSVVMVJ, 79-6060, 79-6061
79-6252, 79-6253, 79-6578

T56 BVNV GUTJ CSXGGG, 79-6157

T6KJ A D- 2 &G &G &3/14 &3/17
79-6187

T6M DOTJ, 79-6057, 79-6180

T6MNJ, 79-6148

T6MPOTJ BO BN2G2G, 79-6009
79-6161, 79-6191, 79-6466, 79-6580

T6MVNJ DZ E1, 79-6425

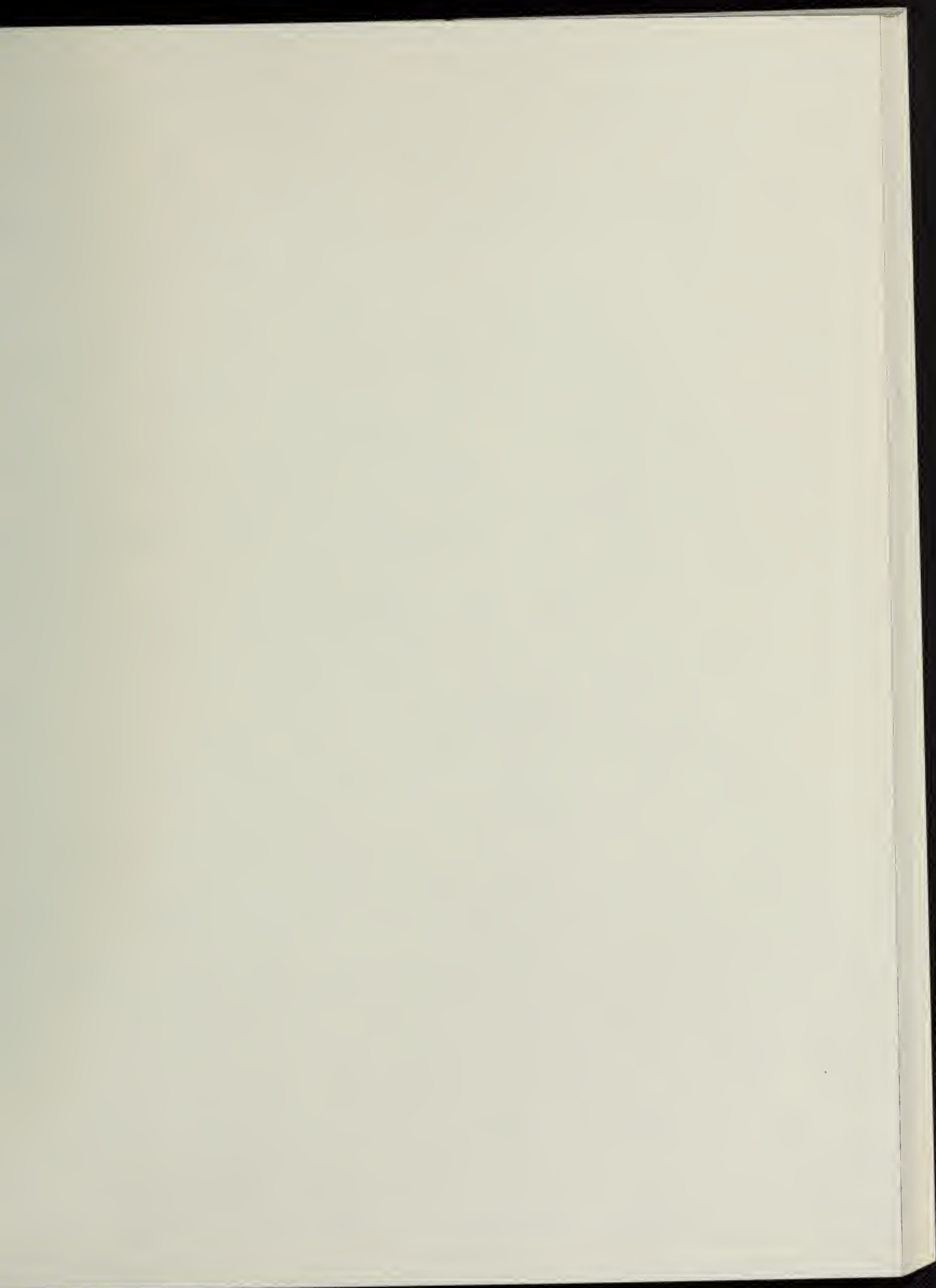
T6N DNTJ A1 DNO, 79-6165

T6N DNTJ A1 DNO (cont'd)
T6N DOTJ ANO, 79-6165, 79-6180
79-6182, 79-6215
T6NJ B1 CQ O1Q E1Q, 79-6565
T6NJ C- BT5NTJ A1, 79-6322
T6NJ DVMMY1&1, 79-6141
T6NJ DVMM2VM1R, 79-6141
T6NJ DVMZ, 79-6141
T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C
79-6225, 79-6226, 79-6273, 79-6392
T6NVMVJ EF A- ET5OTJ B1Q CQ
79-6365
T6NVMVJ E1 A- ET5OTJ B1Q CQ -A&C
79-6392, 79-6428
T6O DVJ B1Q EQ, 79-6160
T6O DVJ B1 CO2, 79-6160
T6O DVJ B1 CQ, 79-6160
T6OTJ BOINUNO&1 CQ DQ EQ F1Q-
A&D -D, 79-6146
T6OTJ BQ CQ DQ F1Q EO- BT6OTJ
CQ DQ EQ F1Q -D, 79-6593
T6VMVMV FHJ F2 FR, 79-6047, 79-6048
79-6246, 79-6326, 79-6335
T6VMVMV FHJ F2 FR &-NA-, 79-6248
T6VMVTJ E1YQ- BL6VTJ D1 F1
79-6159, 79-6277, 79-6598
T66 BM DN FN HNJ IS- ET5N ONJ
DNW, 79-6009, 79-6255
T66 BN DN GN JNJ CZ EQ H1MR
DVMMYVQ2VQ, 79-6057
T66 BNJ BO ENW, 79-6224, 79-6227
79-6358
T66 BNJ EMY&3N2&2 IG, 79-6228
79-6229
T66 BNJ JQ, 79-6055
T66 BNTJ BXFFF D1Q- T6 BNJ
&JXFFF, 79-6228
T66 BOVJ, 79-6066
T66 CNNJ BMZ, 79-6254
T66 CO HV AUT&J D1 E1 G1 IVQ JQ
79-6256
T666 BO IO T&J EG FG LG MG
79-6012, 79-6249, 79-6250, 79-6313
79-6327
T666 BO IOT&J, 79-6249
VHH, 79-6059, 79-6163

VHH, 79-6160
WNMYUM&N1&NO, 79-6218, 79-6219
79-6220, 79-6221, 79-6222, 79-6223
79-6224, 79-6466
WNR BG ENW, 79-6298
WS1&OY1&1, 79-6209
WS1&O1, 79-6145, 79-6205, 79-6209
79-6466
WS1&O2, 79-6206, 79-6209, 79-6599
WS1&O2 2U -C, 79-6009
ZM1, 79-6244
ZR BNW DZ, 79-6213
ZR BZ DNW, 79-6213
ZR B1, 79-6241
ZR B1 D- 2, 79-6260
ZR B1 DNUNR B1, 79-6234
ZR CZ, 79-6213
ZR CZ DO1, 79-6167, 79-6235
ZR CZ DO1 &WSQQ, 79-6213
ZR CZ D1, 79-6240
ZR C1, 79-6241
ZR DNUNR, 79-6237, 79-6246, 79-6288
ZR DR, 79-6241
ZR DR DZ, 79-6011, 79-6260
ZR DZ, 79-6237
ZR D1, 79-6241
ZVMQ, 79-6186
ZVMR DNW, 79-6202
ZVN1&NO, 79-6065, 79-6148, 79-6203
79-6204, 79-6205, 79-6206, 79-6208
79-6209, 79-6346, 79-6466
ZVN2&NO, 79-6205, 79-6206, 79-6209
79-6210
ZVN4&NO, 79-6206
ZVO1U1, 79-6020
ZVO2, 79-6020, 79-6110, 79-6187, 79-6198
ZZ, 79-6023, 79-6141
Z1YQR CQ DQ -L, 79-6164, 79-6547
Z2R CQ DQ, 79-6547
Z3Z, 79-6275
1MM1, 79-6174, 79-6175, 79-6176
79-6177

1MR, 79-6245
1MR DNUNR, 79-6237, 79-6246
1NO&UN1R DVMY1&1, 79-6244
1NQR DNUNR, 79-6246
1N1&NUNR, 79-6165
1N1&R, 79-6241
1N1&R C1 DNUNR, 79-6242
1N1&R DNUNR, 79-6005, 79-6247
79-6310, 79-6507
1N1&R DNUNR C1, 79-6236, 79-6237
1N1&R DIU1R, 79-6024, 79-6302
79-6340
1N1&R DIU1R -T, 79-6024, 79-6302
79-6340
1N1&YUS&S 2, 79-6199
1OV9U8, 79-6179
1O2OVR BVO2O1, 79-6006
1UYG1U1, 79-6050, 79-6158
1UIR, 79-6248
1VNQR DR, 79-6173
1VV1, 79-6160
1X1&1&R BQ CX1&1&1 E1, 79-6110
1Y&MVR D1MM1, 79-6243, 79-6244
79-6299
1Y1&MVR DVH, 79-6244
1Y1&1R BQ EO1, 79-6187, 79-6291
79-6301
1Y1&1R CQ FO1, 79-6187, 79-6291
79-6301
2MR, 79-6241
2MR DNUNR, 79-6246
2N2&YUS&S 2, 79-6148
2OR DMV1, 79-6007, 79-6008
2OV1U1VO2, 79-6219, 79-6322
3XR&R&VO2N2&2, 79-6313
3XR&R&VO2N2&2 &GH, 79-6150
4O2OVR BVO2O4, 79-6006
4Y2&1OVR BVO1Y2&4, 79-6006

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VOLUME 17, ISSUE 12

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page Nos.
REVIEW	(Rev)	79-6601—79-6642	2521
CHEMICAL CARCINOGENESIS	(Chem)	79-6643—79-6868	2531
PHYSICAL CARCINOGENESIS	(Phys)	79-6869—79-6925	2578
VIRAL CARCINOGENESIS	(Viral)	79-6926—79-7063	2590
IMMUNOLOGY	(Immun)	79-7064—79-7098	2619
PATHOGENESIS	(Path)	79-7099—79-7137	2627
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	79-7138—79-7185	2636
MISCELLANEOUS	(Misc)	79-7186—79-7200	2646
AUTHOR INDEX			2651
SUBJECT INDEX			2657
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2697
WISWESSER LINE NOTATION INDEX			2701

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		

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REVIEW

- 79-6601 Cancer Development from the Viewpoint of Molecular Biology. (Ger) Popp, F. A. (Radiologiezentrum der Universität, Lahnstrasse 4a, 3500 Marburg, W. Germany). *Krebsgeschehen* 11(2): 48-51; 1979.

The tendency of scientists to adopt a "local" viewpoint in cancer research, ie, to interpret carcinogenesis as a cellular defect rather than as a defect in a tissue as a whole, is criticized, and a theory of "non-local" carcinogenesis is presented. The theory is based on the observation that, within a group of biologically active molecules, the activity depends on resonance-coupling to an electromagnetic (photon) field. This electromagnetic field is considered to be a property of tissue, not of single cells. According to the model, photon-emission (Ph-E) from growing tissue is higher than that from mature tissue. Photon-absorption occurs also, so that equilibrium is maintained. However, dying cells emit, but do not absorb, photons, a condition thought to stimulate repair. Tumor cells are thought to have reduced ability to absorb photons, compared with normal growing tissue. Thus, cancer tissue is on the photon-emitting side of equilibrium. The Ph-E curves of Ehrlich-ascites tumor cells treated with different concentrations of 4-hydroperoxycyclophosphamide show a lack of photon absorption ability, compared with normal cells. The ability of chemotherapeutic drugs to normalize photon absorption in biopsy specimens of a given tumor should be tested; this is recommended as a method of providing more individualized treatment. (28 refs)

- 79-6602 Problems and Perspectives in Perinatal Carcinogenesis: A Summary of the Conference. (Eng) Rice, J. M. (Experimental Pathology Branch, NCI, Bldg. 37, Room 3A09, Bethesda, MD 20205). *Natl Cancer Inst Monogr* (51): 271-278; 1979.

A major stimulus for the study of perinatal carcinogenesis has been the concept that the fetal and neonatal periods are times of high susceptibility to carcinogens. No known carcinogen acts exclusively in the fetus or neonate, but some agents show a greater effect in the fetus or neonate than in the adult. Diethylstilbestrol, for example, induces change in the human fetus leading to carcinogenesis but is not carcinogenic in the adult female. Estrogens are, however, carcinogenic in adult rodents. The state of differentiation of the murine female reproductive tract is critical for the induction of modifications in function by exogenous hormones. High perinatal susceptibility to hormones is inherent in the undifferentiated state, but susceptibility to nonhormonal carcinogens tends to increase with increasing differentiation. Most chemical carcinogens require enzyme-mediated metabolism for conversion to the active state. Decreased fetal response to some carcinogens is due to lack of metabolizing enzymes in fetal tissue. A rapid bioassay involving in utero exposure to a carcinogen followed by cell culture studies to reveal transformed cells has helped elucidate potential in vivo control mechanisms in tumor development. The immune system may either enhance or inhibit these processes. The direct-acting alkylating agents are the most potent transplacental carcinogens, partly because they are independent of enzyme-mediated metabolism. Their carcinogenic effects are often restricted to certain organ systems, and different organ systems are affected in different species. Undifferentiated embryonic tissues are resistant even to these agents. Some human tumors are rarely

found in rodents. An increased tumor risk has been found in offspring of animals treated in utero. The refractory nature of undifferentiated tissue has also been found to apply to oncogenic viruses. Most tumors induced transplacentally or neonatally in rodents are histologically identical to human adult but not infant tumors. It is stressed that more than one species should be studied and comparisons made between these species. (17 refs)

- 79-6603 The Problem of Estimating Safe Dose Levels in Chemical Carcinogenesis. (Eng) Wahrendorf, J. (Institut für Dokumentation, Information und Statistik, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany). *J Cancer Res Clin Oncol* 95(2): 101-107; 1979.

Various methods of determining safe dosages of chemical carcinogens are summarized with respect to models for tumor rates and models for failure times. Three different mathematical models for tumor rates (dose-effect) are discussed in terms of rationale, advantages and disadvantages, and correlation with experimental data. The log-probit model is based on the assumption that there is a tolerance level for a carcinogen that shows a random variation according to a log-normal distribution among the individuals examined. The log-logistic model differs from the log-probit model only in that the logit-transform of the effect shows a linear dependence on the logarithm of the dose. The multi-stage model assumes that the carcinogenic process takes place in an integral number of steps that may be induced spontaneously or as a result of the dose administered; this is expressed mathematically so that the probability of developing a tumor decreases exponentially towards zero with decreasing dose. A table is presented that lists the expected probabilities of response for these three models over a wide dose range. Models for failure time are discussed with regard to the necessity for consideration of the toxicity of a substance and the survival patterns of animals in which it is tested. One example of a stochastic model for failure times is described in detail, with discussion of the probability distribution of time of incidence, the use of the multi-stage model for the dose-dependency, hazard functions, calculation of safe dose, and correlation with simulated studies and animal experiments. Other considerations in the estimation of safe dosages of carcinogens are briefly mentioned and include the following: the difference between animal models and actual human environments, the complexity of carcinogenesis, and necessary features of in vitro and in vivo experiments. (25 refs)

- 79-6604 Can Mutation Theories of Carcinogenesis Set Priorities for Carcinogen Testing Programs? (Eng) Stich, H. F. (Environmental Carcinogenesis Unit, British Columbia Cancer Res. Center, Vancouver, British Columbia, Canada); Acton, A. B. *Can J Genet Cytol* 21(2): 155-177; 1979.

The use of mutation theories of carcinogenesis in setting priorities for carcinogen testing programs is reviewed. A model of carcinogenesis is proposed as a basis for this discussion. Carcinogenesis is envisaged as the loss of regulatory function due to mutations or deletion of specific regulator (*R*) genes followed by

derepression and increased activity of tumor (*Tu*) genes. Mutations are assumed to be the main cause of impairment of *R* gene activity. According to the mutation model, a carcinogen must initiate the process of carcinogenesis by inducing a mutation and must also be present after the original clones are formed to induce gene mutations or chromosome aberrations, thus bringing about an inactivation of remaining *R* genes. Short-term tests that rely on only one endpoint (mutations, chromosome breakage, DNA fragmentation, inhibition of DNA replication) are limited in their scope because they reveal only one facet of carcinogenesis. These tests must be complemented by tests that include other endpoints that are actually a part of neoplastic transformation. Tests for DNA fragmentation, DNA repair, micronuclei, etc, could be adapted for use in human biopsy, surgical, or autopsy specimens. The inclusion of such tests would reveal the organ-specific actions of carcinogens. The design of in vitro test systems capable of detecting and quantitating promoter and anti-promoter actions of chemicals should be given a very high priority. (87 refs)

- 79-6605 The Importance of Frame-Shift Mutations in Carcinogenesis. (Eng) Presber, W. (Inst. Virology, Humboldt-Univ., Schumannstr. 20/21, 104 Berlin, E. Germany); Kruger, D. H. *Fortschr Onkol* 4: 175-179; 1979.

A molecular mechanism of carcinogenesis which encompasses several hypotheses and reconciles certain contradictions is proposed. It is suggested that cancer results from a defect in the cell's molecular regulation and that realization of the cancer information can be explained by a frame-shift mutation. The hypothesis that carcinogenesis occurs as a result of frame-shift mutation is valid for both chemically and virally induced malignant transformation. If a virus were integrated into the host cell DNA without frame shift and it had no function that interfered with the host's gene expression, infection would proceed without transformation. Such silent proviruses could be induced by some chemicals, however, so that frame-shift mutations can be produced indirectly by agents that are not themselves frame-shift mutagens. Based on the proposed model, radiation would act as a carcinogen by causing primary DNA lesions, which would in turn induce repair processes. During repair, frame-shift mutations could occur, and the repair processes could lead to a high frequency of virus integration and thereby cause frame shifts. (34 refs)

- 79-6606 A Theory of Cancer Induction by Parametric Excitation. (Eng) Barrett, T. W. (Dept. Physiology and Biophysics, Univ. Tennessee Center Health Sciences, 800 Madison Ave., Memphis, TN 38163). *Cancer Biochem Biophys* 3(4): 189-192; 1979.

A theory of cancer induction by ultimate carcinogens via parametric excitation is presented. The requirement for energy transfer in the perturbation of DNA is discussed, and the concept of energy transfer by resonance is rejected in favor of energy transfer by parametric excitation, of which resonance is a special case. A remarkable agreement between the Raman vibrational bands of ultimate carcinogens, various hypochromic bands of DNA, and the predictions of parametric excitation theory was observed. The results suggest that the peculiar relation of an ultimate carcinogen and DNA results in a parametrically induced transfer in the vibrational mode. The problem of cancer induction then becomes one of analytical mechanics. This theory offers little hope for the development of a method that would completely prevent cancer induction, but it does offer the possibility of develop-

ing an extremely quick and efficient test of environmental molecules for ultimate carcinogenicity. If a molecule has Raman bands that may parametrically excite a DNA hypochromic band, then that molecule may be assumed to be a carcinogen requiring no metabolic activation for its effect. (30 refs)

- 79-6607 Teratogenic and Carcinogenic Effects of Some Chemicals During Prenatal Life in Rats, Syrian Golden Hamsters, and Minipigs. (Eng) Ivankovic, S. (German Cancer Res. Center, Heidelberg, W. Germany). *Natl Cancer Inst Monogr* (51): 103-115; 1979.

Studies on the teratogenicity and carcinogenicity of alkylnitrosoureas are reviewed. When pregnant rats were treated with ethylurea and sodium nitrite in the second half of gestation, all the offspring died from neurogenic tumors. The median teratogenic dose of ethylnitrosourea (ENU) was 46 mg/kg and corresponded to about one-fifth of the LD₅₀. Teratogenesis was strictly dose-dependent in the Syrian golden hamster and minipig as well as the rat. ENU is also a potent carcinogen in these species, and in mice, when administered prenatally. When administered to rats on day 12 of gestation or later, ENU invariably induced malignant nervous system tumors and, occasionally tumors in the progeny. Tumors with the shortest induction time (190 days) were located in the nervus trigeminus and the ganglion Gasserii. All were rapidly growing neurosarcomas. Malignant tumors of the peripheral nerves were more frequent than those of the brain. The median latency of the peripheral nerve tumors was 215 days; that of the brain tumors was 250 days. Most brain tumors were mixed gliomas. Methylnitrosourea and n-butylnitrosourea were much less active when tested for carcinogenicity, but n-propylnitrosourea was almost as effective as ENU. Simultaneous po administration of L-citrulline and sodium nitrite after day 12 of gestation induced nephroblastomas in 6/22 rat progeny. Fetal tissue was 50 times more sensitive than adult tissue to low doses of the carcinogens. (65 refs)

- 79-6608 Host Factors Affecting Perinatal Carcinogenesis by Resorptive Alkylnitrosoureas in Rats. (Eng) Koestner, A. (Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH 43210); Swenberg, J. A.; Denlinger, R. H. *Natl Cancer Inst Monogr* (51): 211-217; 1979.

Studies of ethylnitrosourea (ENU)-induced perinatal carcinogenesis in rats, mice and hamsters are reviewed. Under optimal conditions, nearly 100% of offspring of rats given ENU inoculations during late gestation developed nervous system tumors. With decreasing doses, the tumor incidence decreases and the latency period increases. Neuroectodermal cells were the target site in rats, but only tumors of the peripheral nervous system were found in hamsters. In mice, the highest incidence of neurogenic tumors (32%) was reported in the C3HeB/Fe strain; in other strains the incidence ranged from 0%-25%. The predominant tumor type also varied with strain. In a study of the transplacental passage of ENU, newborn syngeneic mice were inoculated with brain cell suspensions obtained 1, 4, or 24 hr after the transplacental exposure of CDF rats to ENU (50 mg/kg iv on gestation day 20). Mixed glial tumors developed 10-12 mo later at inoculation sites in 2/11 rats treated with the 1-hr collection and in 1/9 rats treated with the 4-hr collection. Thus, the molecular events of neoplastic transformation took place within 1 hr of ENU transformation. Dimethylnitrosamine (DMN) was effective as a transplacental carcinogen only during the last days of the pregnan-

cy. The neuro-oncogenicity of ENU in the rat increased with advancing pregnancy and culminated at parturition. In mice, however, the incidence of pulmonary tumors was highest when ENU was administered on gestation day 16. Although tumors were not induced by ENU in rat or mouse fetuses before the 12th day, embryotoxicity and teratogenicity were produced. The genetic concept of neoplastic transformation implicates change in the DNA molecule as the principal lesion in tumor induction. A second concept considers transformation to result from derepression of DNA sequences generally suppressed in the normal cell. Immunologic surveillance protects against bladder tumors but not neuroectodermal tumors in rats. However, tumor-specific transplantation immunity was found in syngeneic rats immunized and challenged with cells from a methylnitrosourea-induced brain tumor. (44 refs)

- 79-6609 Neoplastic Response of Mouse Tissues During Perinatal Age Periods and Its Significance in Chemical Carcinogenesis. (Eng) Vesselinovitch, S. D. (Dept. Radiology, Pritzker Sch. Medicine, Univ. Chicago, Chicago, IL 60637); Rao, K. V.; Mihailovich, N. *Natl Cancer Inst Monogr* (51): 239-250; 1979.

Studies of chemical carcinogenesis in perinatal mice are reviewed. (C57BL/6J x C3HeB/FeJ)F₁ mice were treated ip with ethylnitrosourea (ENU: 60 µg/g) prenatally (day 12-18 of gestation), neonatally (day 1), or at the age of 15, 18, or 42 days. The carcinogenicity of perinatal exposure to diethylnitrosamine, benzo(a)pyrene, aflatoxin B₁, DDT, dieldrin, and safrole was also studied. The most important modulator of carcinogenesis in the liver, lung, stomach, ovary, and lymphoreticular tissues was age at time of carcinogen exposure. Infancy was the most susceptible period. Depending on the carcinogen, the pattern of tumor development in different organs varied according to the enzymatic competence of tissues to activate and metabolize the agent. ENU, a spontaneously activated carcinogen, induced 59 types of primary tumors in 22 tissues. In contrast, exposure during infancy to procarcinogens requiring enzymatic activation led to tumors only at a limited number of sites. All carcinogens induced liver tumors. The character of the tumors depended on the carcinogenicity of the agent and the age at treatment. Perinatally induced primary liver tumors grew more aggressively and were more readily transplantable to isogenic hosts than tumors induced at later ages. Since susceptibility to carcinogens is greatest early in life, this perinatal bioassay may be a useful model for prescreening potential human carcinogens, especially when only small amounts of the test substance are available. (84 refs)

- 79-6610 The Significance of the Hamster Model in Carcinogenesis Testing. (Eng) Grandjean, C. J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE 68105); Althoff, J. *Prog Exp Tumor Res* 24: 207-214; 1979.

Based on data from previous studies, the carcinogenicities of vinyl ethylnitrosamine (VEN) and diallylnitrosamine (DAN) for Syrian golden hamsters were compared with those for BD rats. VEN, a somewhat weak carcinogen in rats, was highly potent in hamsters in terms of toxicity, tumor latency and multiplicity, organs affected, and total dose required. In all instances, the hamster was more susceptible. DAN, which is noncarcinogenic in rats, produced a 100% tumor incidence in hamsters, affecting primarily the respiratory system. A significant number of tumors were induced by a single dose of DAN. A fundamental species dif-

ference appears to be responsible for the different biological responses to these two compounds. Of approx 100 N-nitrosamines which have been found to cause tumors in at least one species, some appeared devoid of or low in carcinogenic activity in rats only. (6 refs)

- 79-6611 Model Studies in Tobacco Carcinogenesis with the Syrian Golden Hamster. (Eng) Hoffmann, D. (Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY 10595); Rivenon, A.; Hecht, S. S.; Hilfrich, J.; Kobayashi, N.; Wynder, E. L. *Prog Exp Tumor Res* 24: 370-390; 1979.

The use of the Syrian golden hamster (SGH) as a model for the study of tobacco carcinogenesis is reviewed. The SGH has a lower rate for spontaneous lung tumors than other rodents, and its respiratory tract more closely resembles that of man. Special smoking devices have been developed for the passive inhalation of cigarette smoke by hamsters. Since only a small portion of the carcinogenic smoke particulates reaches the trachea and bronchi, tumors are rarely seen in the lung, most histopathologic changes occurring in the larynx. These changes range from hyperplasia to papillomas and occasional carcinomas. In susceptible inbred lines of SGH, high incidences of laryngeal carcinoma occur. The smoke of experimental cigarettes which produces 'tar' with reduced carcinogenic activity in mouse skin also shows reduced tumorigenicity for the hamster larynx. During curing and smoking of tobacco, N'-nitrosornicotine is formed from nicotine and nornicotine; and N-nitrosodiethanolamine is formed from diethanolamine, a solubilization agent used to spray tobacco. Both nitrosamines induce papillomas in the trachea and carcinomas in the nasal cavity of the SGH. (42 refs)

- 79-6612 Carcinogenesis of N-Nitroso-Morpholine and Derivatives in Syrian Golden Hamster. (Eng) Mohr, U. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany). *Prog Exp Tumor Res* 24: 235-244; 1979.

Carcinogenicity studies of seven cyclic nitrosamines in Syrian golden hamsters are reviewed. Nitroso-acetidine, which is carcinogenic for rats and mice, produced no tumors when administered in the drinking water to hamsters. Inhalation of nitroso-pyrrolidine also produced no tumors in hamsters although an organotropic effect in the lungs was evident following sc administration. Nitroso-piperidine (NP) produced tracheal tumors, papillary polyps, and papillomas in hamsters. Tumor latency was increased by decreasing the frequency of administration, and decreases in dosage resulted in reduced tumor incidences and increased survival times. A single dose of 0.075 of the LD₅₀ induced tracheolaryngeal neoplasms in 20% of the hamsters treated. Administration of NP (100 mg/kg body wt, sc) to pregnant females resulted in a 0%-7% incidence of respiratory tract tumors in the offspring. Results obtained after sc nitroso-morpholine (NM) administration (80 mg/kg body wt/wk) were similar to those seen with NP, but with a higher incidence of nasal cavity tumors and some bronchogenic adenomas in the lungs. The tumor latency following a single dose of NM was shorter than that following a single dose of NP. Nitroso-2,6-dimethylmorpholine was less toxic than NP and considerably more toxic than NM. It produced respiratory tumors in 100% of the treated animals and also induced tumors of the upper digestive tract, liver, and pancreas after as little as 15 wk. The sites of tumor involvement varied with dif-

ferent routes of administration. The main target of sc nitroso-hexa-methyleneimine was the trachea, but tumors also developed in the nasal cavities and lungs. Oral nitroso-hepta-methyleneimine treatment resulted in a high incidence of upper digestive tract tumors and a significant number of upper respiratory tract tumors. (16 refs)

- 79-6613 The Case of Dapsone. News About Carcinogens: What's Fit to Print? (Eng) Bloom, B. R. (Dept. Microbiology, Albert Einstein Coll. Medicine, New York, NY). *Hastings Cent Rep* 9(4): 5-7; 1979.

Studies on the carcinogenicity of diamino-diphenylsulfone (dapsone), a drug used to treat leprosy and to prevent the emergence of chloroquine-resistant malaria, are reviewed in response to the release of a report by NCI that dapsone caused cancer in rats. In a standard animal carcinogenicity test, dapsone, given at the max tolerated dose, failed to cause an increased incidence of cancer in male or female mice, or in female rats, but did produce a significant increase in cancer incidence in male rats. A number of flaws in the design of the study weaken the validity of these results. However, another, better-designed study also showed a significant increase in the same kind of cancer, again only in male rats. It was concluded in this study that carcinogenesis was probably a secondary effect of fibrosis and tissue damage caused by dapsone. Dapsone and its known human metabolites and breakdown products failed to increase bacterial mutations in the Ames test. Three studies on patients treated with the drug for long periods because of leprosy have failed to show higher incidences of cancer compared with control groups. (3 refs)

- 79-6614 Toxicity of Spices Containing Methyleneedioxybenzene Derivatives: A Review. (Eng) Buchanan, R. L. (Dept. Nutrition and Food Sciences, Drexel Univ., Philadelphia, PA 19104). *J Food Saf* 1(4): 275-293; 1978.

The current data on the potential carcinogenicity of methylenedioxybenzene derivatives in spices are reviewed; and the properties of safrole, isosafrole, dihydroxysafrole, β -asarone, estragole, myristicin, elemicin, apiol, dillapiol, eugenol, piperine, capsaicin, and anethole are discussed. The identification of safrole (1-allyl-3,4-methylenedioxybenzene; found in black pepper, nutmeg, mace, star anise oil, cinnamon leaf oil, cocoa, and parsley), isosafrole, dihydroxysafrole (a metabolic derivative of safrole), β -asarone (used as a bitter flavor), and estragole (found in tarragon, fennel, basil, and turpentine) as weak carcinogens suggests that spices containing other methylenedioxybenzene derivatives or other closely related aromatic compounds should be investigated for carcinogenicity (particularly spices containing anethole, myristicin, apiol, dillapiol, piperine, eugenol, or methyl eugenol). (55 refs)

- 79-6615 Chronic Interstitial Nephritis as a Cause of Tumors of the Upper Urinary Tract. A Hypothesis. (Eng) Sorrentino, F. (Riviera di Chiaia, 207, I-80121 Naples, Italy); De Martino, A. M. *Urol Int* 34(6): 393-402; 1979.

Data supporting the hypothesis that chronic interstitial nephritis is the single common cause for the high incidence of upper urinary tract tumors in cases of phenacetin abuse, endemic nephropathy, or infected pyelic calculi are reviewed. For a carcinogen to be ef-

fective, it must be discharged in the urine in high concentrations and absorbed by the urothelium, remaining there for some time before excretion. It is hypothesized that interstitial nephritis, by slowing reabsorption through pyelo-lymphatic reflux and by impeding the lymphatic drainage of the pyelic and ureteral walls, leads to a prolonged intra-tissue stasis, thereby enhancing the effect of carcinogens. If this hypothesis is correct, a high incidence of upper urinary tract tumors should be observed in dialysis and renal transplant patients. (39 refs)

- 79-6616 Reactive Metabolites of Xenobiotics: Their Role in the Hepatotoxicity of Drugs. (Fre) Pessayre, D. (Unite de Recherches de Physiopathologie Hepatique (INSERM), Hopital Beaujon, 92118 Clichy, France); Benhamou, J. P. *C R Soc Biol (Paris)* 173(2): 458-468; 1979.

Studies of the metabolism and hepatotoxicity of drugs and the induction of microsomal enzymes are reviewed. Certain drugs are transformed into reactive metabolites by cytochrome P-450. The reactive metabolites bind covalently to hepatocytic macromolecules, thereby causing hepatic lesions. Induction of microsomal enzymes enhances the formation of reactive metabolites and increases the hepatotoxicity of these drugs. Compounds that form unstable reactive metabolites include chloroform, halothane, trichloroethylene, acetaminophen, phenacetin, cyclophosphamide, urethane, imipramine, iproniazide, natural estrogens, ethinylestradiol, norethynodrel, α -methyl dopa, and isoniazide. Isoniazide is first metabolized to acetylhydrazine, then to an unstable metabolite that binds irreversibly to hepatic proteins. (19 refs)

- 79-6617 Cell Culture as a Test System for In Vitro Detection of Carcinogenic Material. (Ger) Seemayer, N. (No affiliation given.). *Lufthyg Silikoseforsch* 11: 65-80; 1978.

The use of cultured cells for in vitro testing of chemicals for carcinogenesis is reviewed. The ability to produce malignancy in animals (usually *nu/nu* mice) is still the most valid evidence that transformation has occurred in culture. Golden Syrian hamster embryo cells were used as early successful models of carcinogenesis. These studies indicated that chemical carcinogenesis is a one-step process and that toxicity does not correlate with carcinogenesis. In a study of 120 compounds, correct identification of carcinogenicity in 90% of the tests was found only for the Ames test and the cell transformation test (CTC), although four other quick in vitro tests were evaluated. Fibroblasts from mouse prostates have been used to develop a test that is especially useful for testing polyaromatic compounds. The test requires at least 6 wk. A cocarcinogenic effect of particulate material from air has been shown with rat or hamster cells previously infected with an oncogenic virus. In vitro transformation of human cells by viruses and by chemicals has been reported. Current evidence from in vitro studies favors induction of transformation rather than selection of previously transformed cells as the mechanism of chemical carcinogenesis. (56 refs)

- 79-6618 Prenatal Exposure to Chemical Carcinogens and Its Effect on Subsequent Generations. (Eng) Tomatis, L. (International Agency Res. on Cancer, 150, cours Albert-Thomas, 69372 Lyon, Cedex 2, France). *Natl Cancer Inst Monogr* (51): 159-184; 1979.

Evidence that transplacental carcinogens can increase tumor incidence in untreated animals of the second and third generations is reviewed. In one experiment, 7,12-dimethylbenz[a]anthracene (DMBA: 350 or 500 μ g) was given ip to outbred Swiss mice a few days to 12 hr before delivery. Five females of the first generation (F_1) whose mothers had received 350 μ g DMBA were mated with their brothers to obtain the second generation (F_2). An increased incidence of tumors was observed in both the F_1 and the F_2 progeny. In the second generation tumor incidence was higher in females than males. The tumors involved mainly the mammary glands and ovaries in females, the paraurethral and lachrymal glands in males, and the lungs in both sexes. Similar studies with methylnitrosourea and ethylnitrosourea in rats showed that exposure to the carcinogens during pregnancy resulted in a high incidence of tumors in F_1 animals, and an increased incidence of tumors at specific sites in animals of the second and third generations. The administration of dichlorodiphenyltrichloroethane to CF-1 mice for five consecutive generations did not result in an increased incidence of tumors. It is suggested that the tumors observed in animals of the second and third generations occurred (1) as a consequence of a mutation at a specific locus or (2) as the result of interactions between environmental factors and an inherited lesion that did not produce cancer by itself. (98 refs)

79-6619 Incorporation of Transplacental Exposure into Routine Carcinogenicity Bioassays. (Eng) Swenberg, J. A. (Chemical Industry Inst. Toxicology, P. O. Box 12137, Research Triangle Park, NC 27709). *Natl Cancer Inst Monogr* (51): 265-268; 1979.

Theoretical and practical aspects of experimental transplacental and neonatal exposures to carcinogens are discussed and reviewed. Perinatal carcinogenesis has been demonstrated in humans and seven other species (mouse, rat, hamster, guinea pig, rabbit, pig, and opossum). Sensitivity of the fetus or neonate varies from 100x that of the adult to much less than that of the adult. Some compounds, like diethylstilbestrol, may only cause tumors transplacentally. A typical carcinogenesis protocol that incorporates transplacental and neonatal exposure utilizes 50-55 animals per sex per dose exposed to the test compound for 24 mo. Three dose-levels and controls are ordinarily used, with the highest dose being the max tolerated dose that does not reduce life-span or induce excessive wt loss. Exposure to the drug po usually begins on the 15th day of gestation in rats and mice; the time of first exposure is adjusted if other species are used. Chemicals that induce abortion, prevent delivery, or interfere with lactation cannot be tested by this protocol. Dosing of the pregnant female continues through parturition and weaning. For the latter part of the study, dosing of the neonate by gastric intubation is preferred. After weaning at 3-4 wk, the offspring are exposed by either mixing the compound with the food or water or by intubation. Usually, a minimum of 25 date-mated females are exposed per dose level, and 2 males and 2 females are selected from the litter to reduce inter-litter variation. Compounds to which pregnant women are likely to be exposed should receive priority for the combined transplacental-neonatal-conventional exposure type of bioassay. Short-term assays, many of which use in vivo-in vitro systems, may be utilized to determine such priorities. (6 refs)

79-6620 Perinatal Carcinogenesis: Biologic Curiosity or Practical Necessity? (Eng) Clayson, D. B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NE 68105). *Natl Cancer Inst Monogr* (51): 235-238; 1979.

The question of whether transplacental carcinogenesis should be included in rodent carcinogen bioassays is discussed. Perinatal carcinogenesis is not believed to differ fundamentally from carcinogenesis in the adult animal. Some differences, however, must be taken into account. Conversion of a precarcinogen to a reactive electrophile may occur in either the mother or fetus, and different tissues and processes may be involved in each case. The simplest test of fetal exposure would be to demonstrate the presence of the carcinogen or a metabolite in the fetus. Studies of carcinogen interactions with cellular macromolecules would be a more specific approach. More applicable results may be obtained from an examination of the metabolic capabilities of specific fetal tissues, the placenta, and the mother. The activities of metabolizing enzymes vary widely, and these variations should be considered. An additional possibility is that an ultimate carcinogen activated in maternal tissue may be too unstable to reach the fetus in concentrations sufficient to induce tumors. The time of pregnancy at which transplacental carcinogens are administered is also critical. Generally, these substances lead to embryotoxicity early in pregnancy, to teratogenicity later, and carcinogenesis late in pregnancy. Cell proliferation during development may enhance carcinogenicity. Known perinatal carcinogens such as diethylstilbestrol should be retested to determine their mechanism of action. Most classes of chemical carcinogens include perinatal carcinogens; ie, polycyclic aromatic hydrocarbons, aromatic amines and aminoazo compounds, nitrosamines, mycotoxins, hormones, and miscellaneous compounds like urethan. Among chemicals that should be tested transplacentally, drugs, including oral contraceptives and substances used in disease control programs, deserve the highest priority. Food additives are the second concern. General environmental contaminants have the lowest priority. Results of such studies may identify carcinogens not found in tests on adult animals. (29 refs)

79-6621 The Biologic Effectiveness of Ultraviolet Light. (Eng) Rupert, C. S. (Programs in Biology, Univ. Texas Dallas, P.O. Box 688, Richardson, TX 75080). *Natl Cancer Inst Monogr* (50): 85-89; 1978.

The biologic effects of visible and UV light result from photochemical changes in cell components. The amount of photochemical change induced in a small non-self-shadowing structure is proportional to the number of photons traversing it per unit area normal to the direction of propagation, summed over all component beam directions. Within an optically complex, absorbing, and scattering structure, this quantity is difficult to determine, but for skin it is approx proportional to the total number of photons per unit area entering its outer surface. The magnitude of some photobiologic effects depends on the total number of photons per unit area entering its outer surface. The magnitude of some photobiologic effects depends on the total amount of photochemical change induced, whereas others depend on the rate of photoproduct formation or on a more complex relation. The nature of the dependence must be determined before light measurements can be related to the magnitude. The effect of a polychromatic illumination depends on its wavelength distribution, weighted by the effectiveness of each wavelength (the action spectrum) under the conditions employed. Until the latter is known, no dosimetric characterization of the light is possible. The wavelength distribution can be determined by spectroradiometric measurement, with the weighting performed numerically, or (more conveniently, though less accurately) by the use of an analog reaction with an action spectrum like that of the photobiologic effect. (13 refs)

- 79-6622 Multiple Pathways of DNA Repair and Their Possible Roles in Mutagenesis. (Eng) Smith, K. C. (Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305). *Natl Cancer Inst Monogr* (50): 107-114; 1978.

Current knowledge on the multiple pathways of the various types of DNA repair is reviewed, and, when possible, the pathways are classified as being either error-free or error-prone. In studies on bacteria, the excision repair of UV-radiation-induced DNA base damage has been divided into two major pathways on the basis of physiologic requirements and genetic control. The major pathway requires a functional *polA*⁺ gene, does not need complete growth medium, is largely error-free, and produces short patches during repair. The second pathway requires complete growth medium and functional *recA*⁺, *recB*⁺, *recC*⁺, *lexA*⁺, *uvrD*⁺, and *polC*⁺ genes; is mutagenic; and produces long patches during repair. A second type of excision repair exists, in which the modified base is removed by a DNA glycosylase, and the chain is nicked by an apurinic (apyrimidinic) acid endonuclease. Subsequent events are presumed to be similar to the above excision repair process. The postreplication repair system has been divided into at least four distinct pathways, three of which depend on functional *recB*⁺, *lexA*⁺, and *uvrD*⁺ genes, and are error-free. A fourth pathway depends on the above gene products but is blocked by postirradiation treatment with chloramphenicol, and may be the UV-inducible, error-prone, mutagenic pathway of repair ("SOS repair"). A possible fifth pathway is dependent on a functional *recF*⁺ gene and is independent of the *recB*⁺-dependent pathways. Mutagenesis is the result of error-prone DNA repair, and evidence is growing that carcinogenesis is also the result of error-prone repair. Therefore, a complete understanding of DNA repair is crucial to a complete understanding of the molecular basis of carcinogenesis. (72 refs)

- 79-6623 Mutagenesis and Cell Transformation by Ultraviolet Irradiation: Many Hypotheses for Few Results. (Eng) Radman, M. (Department Biologie Moleculaire, Universite Libre Bruxelles, B-1640 Rhode-Saint-Genese, Belgium); Spadari, S.; Villani, G. *Natl Cancer Inst Monogr* (50): 121-127; 1978.

UV light-induced mutagenesis in bacteria is a genetically controlled process that is dependent on the induction of some cellular functions, initially provoked by unrepaired photolesions in DNA. Experiments on the extent and fidelity of in vitro DNA synthesis on UV-irradiated templates by bacterial and mammalian DNA polymerases have attributed a crucial role in UV mutagenesis to the polymerase-associated 3' to 5' exonuclease activity. This implies that purified mammalian DNA polymerases α , β , and γ should be able to elongate DNA chains past pyrimidine dimers. A unified working hypothesis for mutational- and virus-induced cancer that involves two-stage carcinogenesis, ie, initiation by mutagens and the subsequent promotion by essentially non-carcinogenic promoters, is proposed. The model assumes the activation of an inducer protease. At effective mutagenic and carcinogenic doses, UV light damages nucleic acids almost exclusively, and the deficiency in a repair system that removes UV-induced pyrimidine dimers from the cellular DNA is accompanied by the mutation- and cancer-proneness to UV light. (52 refs)

- 79-6624 Interaction of Light and Chemicals in Carcinogenesis. (Eng) Davies, R. E. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140). *Natl Cancer Inst Monogr* (50): 45-54; 1978.

The effects of interactions between chemicals and UV light on the carcinogenic process are examined in terms of the three-component system: chemical, light, and biologic target. Various two-component interactions, in addition to unique three-component interactions, are considered. Available information is incomplete concerning such possibilities as promotion by non-carcinogenic light, the contribution of acute or chronic phototoxic events to chemical or physical carcinogenesis, and the relationship between either photochemical carcinogenesis or chemically enhanced photocarcinogenesis and demonstrable phototoxic activity. Interactions such as optical absorption by, or photochemical alteration of, chemicals are considered primarily as confounding variables in experimental situations. It is argued that realities of human exposure may reduce the complexity of these problems in practical safety or regulatory considerations. (35 refs)

- 79-6625 Summary, Perspective, and Closing Remarks. (Eng) Urbach, F. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140). *Natl Cancer Inst Monogr* (50): 199-201; 1978.

Papers presented at a recent international conference on UV carcinogenesis are reviewed. Epidemiologic evidence strongly indicates that sunlight and particularly UV radiation are important in the etiology of human skin cancer. UV wavelengths <320 nm comprise the primary carcinogenic stimulus. Varying the dose rate while keeping the total amount of radiation given per day constant resulted in major variations in carcinogenicity, as did altering the spectrum slightly in a polychromatic UV source. Thus, the assumption that the carcinogenic effects of various UV wavelengths are linearly additive is incorrect. Fractionating the UV dose while keeping the dose rate constant had little effect on carcinogenicity. The interaction of light and chemicals, the microscopic and ultrastructural features of UV-induced skin tumors, UV-induced oncogenic transformation in vitro, and the roles of the various pathways of DNA repair on mutagenesis and cell transformation were discussed. Mutagenesis may apparently result from error-prone DNA repair. Other topics of discussion included the production and measurement of UV light, the effects of heat, humidity, and wind on UV carcinogenesis, and immunologic parameters of UV carcinogenesis. Further evidence for the relationship between cumulative UV exposure and nonmelanoma skin cancer in white-skinned people was presented, and it was shown that malignant melanoma of the skin is related to UV exposure in a different way. In the etiology of malignant melanoma, other major causal effects appear to interact with the UV effects. (15 refs)

- 79-6626 Summary: Repair Processes and Their Role in Carcinogenesis. (Eng) Sutherland, B. M. (Dept. Biology, Brookhaven Natl. Lab., Upton, Long Island, NY 11973). *Natl Cancer Inst Monogr* (50): 151-157; 1978.

Two major aspects of DNA repair and its relationship to carcinogenesis were addressed: the identification of a premutagenic lesion in bacterial cells, whether such a lesion is in mammalian cells, and the relationship of such a lesion and carcinogenesis; and, second, having identified such a chemical alteration, the identification of biological and biochemical steps leading from chemistry to carcinogenesis. The limitations of extrapolation from prokaryote to eukaryote are emphasized. Evidence has been presented indicating that mutagenesis and probably carcinogenesis are due to errors in DNA repair. A general discussion is presented in which clarification of the above points is attempted. (no refs)

- 79-6627 **Ultraviolet Radiation and Skin Cancer in Mice and Men: Accumulation of Effect and Uncertainty of Prediction.** (Eng) Blum, H. F. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140). *Natl Cancer Inst Monogr* (50): 11-12; 1978.

Studies performed 35 yr ago in mice exposed to repeated doses of UV radiation, as well as recent epidemiologic investigations and measurements of carcinogenic radiation in patients with nonmelanoma skin cancer, are reviewed. These studies showed that repeated doses accumulated. The effects of factors such as genetics, human behavior, skin type, and variation in intensity of sunlight cannot be evaluated quantitatively because of their uncertainty. The possibility of inherent indeterminacy must be kept in mind in the study of effects of sunlight. (2 refs)

- 79-6628 **Speculations on the Role of Ultraviolet Radiation in the Development of Malignant Melanoma.** (Eng) Kripke, M. L. (Cancer Biology Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701). *J Natl Cancer Inst* 63(3): 541-548; 1979.

Evidence implicating UV radiation as an etiologic or contributing factor in malignant melanoma is reviewed. Analysis of skin cancer incidence by age and geographic location in the US suggests that both melanoma and nonmelanoma skin cancers are more prevalent in locations receiving high levels of UV exposure. However, melanoma, unlike other skin tumors, may not be related to the cumulative lifetime exposure to UV radiation. There is little doubt that melanoma of the lentigo maligna type is directly related to chronic exposure to sunlight. Some evidence from animal studies supports the existence of other associations between UV malignant melanoma: (1) UV could act as an initiator of malignant transformation that requires additional promotion for expression of the disease (there is no direct evidence to support this possibility, however); (2) UV light could function as a promoter; and (3) UV light may produce a systemic alteration conducive to tumor growth. Some human melanomas possibly occur without any participation of UV radiation, and most experimental melanomas fall into this category—some are genetically regulated, some chemically induced, and some spontaneous. Human melanomas might have in common only the cell affected in the neoplastic process. Additional division of human melanomas into subgroups based on biologic behavior, histologic features, and antigenic properties may permit the assignment of etiologic agents to particular categories of melanoma. (37 refs)

- 79-6629 **Defective Repair of γ -Irradiated DNA in a Case of Xeroderma Pigmentosum.** (Eng) Mikhelson, V. M. (Acad. Sciences USSR, Inst. Cytology, Leningrad, USSR). *Fortschr Onkol* 4: 157-171; 1979.

The results of studies of DNA repair processes in mutants defective in different steps of repair are reviewed. Human mutations that lead to deficiencies in γ -damaged DNA repair include a form of xeroderma pigmentosum (XP), XP II, as well as progeria and ataxia telangiectasia. Diseases involving defects in DNA or chromosome repair fall into three categories: those with the nosological name XP; those united as "chromosomal breakage syndrome"; and those of premature senility. The clinical manifestations in a 22-yr-old Russian woman with XP II are discussed. Although she is the only XP patient described with a

defect in γ -injured DNA repair, other patients with increased sensitivity to ionizing radiation may also have had XP II. Following irradiation, the single-strand breaks in the DNA of the XP II lymphocytes from the above patient failed to rejoin. UV-induced unscheduled DNA synthesis was decreased in both XP and XP II lymphocytes, and XP II cells that were unable to rejoin γ -induced single-strand DNA breaks showed considerably reduced γ -induced unscheduled DNA synthesis. The data suggest that there is a DNA polymerase defect in XP II. The percentage of dicentric and rings in the chromosomes of γ -irradiated XP II cells was similar to that in XP cells and normal cells, and the chromosomes of XP II cells did not differ significantly from those of classic XP in UV-sensitivity. XP II lymphocytes did not differ from those of classic XP or normal cells in the rate of spontaneous chromosome aberrations. (77 refs)

- 79-6630 **Malignant Transformation In Vitro: Criteria, Biological Markers, and Application in Environmental Screening of Carcinogens.** (Eng) Borek, C. (Radiological Res. Lab., Dept. Radiology, Cancer Center, Columbia Univ., Coll. Physicians and Surgeons, 630 W. 168th St., New York, NY 10032). *Radiat Res* 79(2): 209-232; 1979.

Criteria for and biological markers associated with malignant transformation in vitro are reviewed, as is the application of environmental screening of carcinogens. Biological markers which distinguish malignantly transformed fibroblasts from their normal counterparts include pleomorphic morphology, lowered requirement for nutritional factors, loss of density inhibition of growth, complex topography as discernible by scanning electron microscopy, loss of surface proteins, incomplete glycosylation of membrane glycolipids and glycoproteins, increased production of specific proteases, decreased organization of the cytoskeleton, and acquisition of neoantigens. Several of these markers are not consistently found in transformed epithelial cells and therefore cannot serve to distinguish unequivocally neoplastic epithelial cells from their normal counterparts. The only criteria associated with transformation of both fibroblasts and epithelial cells are the ability of the cells to proliferate in semisolid medium and the ability to induce tumors in appropriate hosts. In vitro systems represent a powerful tool for screening the mutagenic/oncogenic potentials of physical, chemical, and environmental agents. Fibroblasts rather than epithelial cells are preferred for this purpose because of the clear-cut phenotypic differences between the normal and transformed cells. These systems have been useful in establishing that malignant transformation can be induced by as little as 1 rad of x-rays or 0.1 rad of neutrons, and that fractionation at low dose levels leads to enhanced transformation. They have also been useful in identifying a large number of hazardous chemicals and in evaluating the relationship between the mutagenic and carcinogenic potentials of radiation and chemicals. (104 refs)

- 79-6631 **Is Cholecystectomy a Predisposing Factor in the Genesis of Colorectal Carcinoma?** (Ger) Peters, H. (Abteilung Chirurgie, Medizinische Fakultät der Technischen, Goethestrasse 27-29, 5100 Aachen, W. Germany); Keimes, A. M. *Dtsch Med Wochenschr* 104(45): 1581-1583; 1979.

Evidence that cholecystectomy increases the risk of colorectal carcinoma (CRCA) is reviewed. Among 779 patients with CRCA, 42 had undergone cholecystectomy previously (Group CX). The age at diagnosis of CRCA in Group CX was approx 10 yr younger than that of the patients who did not undergo cholecystectomy.

The distribution of tumor sites differed in Group CX, with a higher frequency in the transverse and ascending colon and a lower frequency close to the rectum. Group CX cancers were more likely to be undifferentiated. Reasons for the possible association of CRCA and cholecystectomy are discussed. A high intake of fat, cholesterol, and protein is associated with gallstone development and may also increase the risk of CRCA. One study showed a fall in B- and T-lymphocyte numbers and a decreased response to antigen after cholecystectomy. Removal of the gallbladder can cause changes in bile acid (BA) metabolism. After surgery, BA's enter the colon continuously instead of periodically (after eating). Deoxycholic acid, which is carcinogenic in mice, is the main BA after surgery but not in intact persons. 1,2-Dimethylhydrazine-induced colon cancer is more frequent in cholecystectomized mice than in intact mice. Gallbladder mucosa can reabsorb some BA metabolites as relatively inactive glycosides; a fraction of these are excreted in urine. These considerations may partly explain the increasing incidence of CRCA in West Germany. (22 refs)

- 79-6632 The Role of Inert Particles in Malignant Transformations: A Hypothesis of Carcinogenesis. (Eng) Ecanow, B. (Univ. Illinois Medical Center, 833 South Wood St., Chicago, IL 60680); Gold, B. H.; Kohn, D. B.; Ecanow, C. *Physiol Chem Phys* 11(2): 97-107; 1979.

The role of inert particles in malignant transformation is reviewed and a hypothesis of carcinogenesis is proposed. Controlled cellular growth exists in an aqueous matrix that undergoes a spectrum of reversible solvent and structural conformational changes. In contrast, malignant tumor formation occurs in an irreversible non-polar aqueous matrix (coacervate), meaning that in a physicochemical sense uncontrollable cell growth exists in a hydrocarbon-like milieu. It is proposed that foreign insoluble particles which locate on cellular surfaces can induce such coacervate structuring. Resultant formation of abnormal film matrices could initiate pathological transformations in the morphology, metabolism, and replication of the affected cells. This abnormal matrix formation may be a critical factor in the development of malignancies, in both the avascular and vascular stages. It would follow that drugs or other agents capable of disrupting coacervated water matrices could be effective in the treatment of cancer. (26 refs)

- 79-6633 Experimental Data Concerning the Question of the Synergic Action of the Influenza Virus and of Some Chemical Carcinogens in the Pathogenesis of Lung Cancer. (Eng) Sula, J. (2nd Dept. Medical Chemistry and Biochemistry, Charles Univ., 128 53 Prague, Czechoslovakia). *Neoplasma* 26(1): 17-22; 1979.

Information concerning the synergism of the influenza virus (IV) and some chemical carcinogens in the pathogenesis of lung cancer are reviewed. Various oncogenic and nononcogenic viruses have been shown to enhance the development, growth, and malignancy of hydrocarbon-induced tumors. In other experiments, the incidence of lung neoplasms was much higher in mice that received IV intranasally plus urethane ip than in those treated with either agent alone. A more marked proliferative response was observed in human embryonic lung cultures treated with both agents than in those treated with either agent alone, and cell transformation occurred in 48/55 cultures. In C57B mice exposed to three strains of IV (PR-S, B, and Sendai) plus carcinogenic hydrocarbon aerosols, cigarette smoke, or 3,4-benzpyrene, a progression from an initial

proliferative response through squamous metaplasia to squamous carcinoma was observed; no squamous carcinoma developed in controls treated with either virus or carcinogen alone. Lung tumors developed in 78.2% of XMR1 mice treated with IV A₂-Bethesda intranasally plus diethylnitrosamine (DEN) in the drinking water, 58% of mice treated with IV A-PR8 plus DEN, and 10% of mice given DEN only. The frequencies of gastric and hepatic carcinomas did not differ between animals treated with virus plus DEN and those given DEN alone. The mechanism of synergistic action between viruses and carcinogens may involve: (1) impairment of the host's immunologic response to the virus by the chemical or to the chemically induced tumor by the virus; (2) alteration of susceptibility to viral infection by the chemical or of the detoxification mechanism of the cell by the virus; (3) chemically induced viral activity or viral enhancement of cell permeability to the chemical; (4) joint action of virus and chemical upon the critical site in the host cell; (5) viral enhancement of mitotic activity; (6) chemical activation of latent viruses; and (7) viral induction of latent tumor cells. (41 refs)

- 79-6634 Restriction Endonucleases, Simian Virus 40, and the New Genetics. (Eng) Nathans, D. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205). *Science* 206(4421): 903-909; 1979.

This paper is the text of the author's Nobel Prize lecture (1978). The use of simian virus 40 (SV40) DNA as a model eukaryotic chromosome for investigating the biochemistry of DNA replication, gene expression, and regulation of genes is discussed. Classical genetic techniques (random mutagenesis and selection of desired phenotypes) led to the isolation of mutants comprising only about 50% of the SV40 genome. The use of site-specific restriction endonucleases made it possible to induce mutations at preselected sites on the molecule and isolate individual mutants without the need for phenotype selection. The methods used to dissect the tiny SV40 genome are directly applicable to more complex DNA molecules that can be isolated in homogeneous form: large viral chromosomes, plasmids, DNA from cellular organelles, and even certain genes in mammalian DNA. The completely general application of restriction enzymes to the analysis of cellular chromosomes depends on recombinant techniques for cloning and amplifying individual DNA fragments from complex mixtures, and the ability to reintroduce active genes into living cells. With these techniques, chemical and functional analysis of the genome of every organism is possible. In time, it should be possible to elucidate the basic regulatory mechanisms used by plant and animal cells, and eventually to understand some of the complex genetic programs that govern the growth, development, and specialized functions of higher organisms. (78 refs)

- 79-6635 Type C Retroviruses as Vectors for Cloning Cellular Genes with Probable Transforming Function. (Eng) Stephenson, J. R. (Viral Genetics Section, Lab. Cellular and Molecular Biology, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Khan, A. S.; van de Ven, W. J.; Reynolds, F. H. *J Natl Cancer Inst* 63(5): 1111-1119; 1979.

The use of type-C retroviruses as vectors for cloning cellular genes and the application of recombinant viruses for isolating cellular genes, including those with transforming potential, and the subsequent insertion of DNA transcripts of such recombinant viral genes into bacterial plasmids are reviewed. Included in the discussion are the following: the biological properties and genomic struc-

ture of type-C retroviruses, recombinant type-C viruses with transforming potential, the expression of type-C helper virus proteins in nonproducer cells, high-mol-wt polypeptides encoded by replication-defective recombinant viruses containing type-C virus structural and nonstructural components, the purification of transforming virus-coded polypeptides from pseudotype virions, replication-defective mammalian recombinant viral genome structure, and the implications of type-C retroviruses as vectors for cloning eukaryotic cellular genes. The data presented establish that nucleic acid sequences of cellular origin can, by genetic recombination, be inserted into type-C retrovirus-genome RNA. Attempts to demonstrate an etiologic involvement of type-C retroviruses in human cancer have not been convincingly successful; however, such studies have generated considerable information regarding the molecular biology of these viruses. Type-C retroviruses now appear to be of greater significance as potential vectors in the cloning of cellular genes associated with tumor induction than as etiologic agents involved in the disease itself. (77 refs)

- 79-6636 **Mutagenesis and Embryonal Carcinogenesis.** (Eng) Knudson, A. G. (Inst. Cancer Res., 7700 Burholme Ave., Philadelphia, PA 19111). *Natl Cancer Inst Monogr* (51): 19-24; 1979.

Germinal mutation to a dominant gene accounts for an estimated 40% of retinoblastomas, 38% of Wilms' tumors, and 22% of neuroblastomas. The hereditary forms of childhood tumors are highly penetrant events in a tiny segment of the population. The nonhereditary forms are rare events ($\leq 1:10,000$ children) in the vast majority of the population. The hereditary tumors occur at an early age and are often multicentric; the nonhereditary tumors occur at a later mean age and are almost always solitary. There is little clinical difference between the two groups. It is postulated that somatic mutation may be involved in both hereditary and nonhereditary childhood tumors. In a model that fits the age-specific occurrence, it is hypothesized that all childhood cancers, whether hereditary or nonhereditary, are initiated by two mutations, one somatic and the other either germinal or somatic. The background incidence rates of these tumors would reflect spontaneous mutation rates in the germinal and somatic cells, which may be increased by mutagens. The gene for one tumor (retinoblastoma) seems to be located on chromosome 13. Clues to the physiopathology of these tumor genes come from consideration of their tissue specificity, their origin from embryonal cells, and their developmental effects. Childhood cancers may be manifestations of the homozygous states of a series of genes concerned with the differentiation of specific embryonal tissues. (26 refs)

- 79-6637 **Clinical Genetics and Pediatric Neoplasms: Pathogenetic and Etiologic Perspectives.** (Eng) Herrmann, J. (Dept. Pediatrics, Medical Coll. Wisconsin, 1700 W. Wisconsin Ave., Milwaukee, WI 53233); Elejalde, B. R. *Natl Cancer Inst Monogr* (51): 7-18; 1979.

The clinical and genetic aspects of childhood solid tumors and leukemias are discussed. Developmental principles and phenomena common to several tumors and tumor syndromes are critically evaluated. Certain tumors can be described in terms of "formal genesis" syndromes (including Wilms' tumor associated with aniridia, hemihypertrophy, or pseudohermaphroditism; DiGeorge syndrome with thymoma; Poland or Down's syndromes with leukemia; and retinoblastoma with secondary tumors);

"phakomatoses" (including tuberous sclerosis, neurofibromatosis, nevoid basal cell carcinoma syndrome, Gardner's syndrome, blue rubber bleb nevus syndrome, and other autosomal dominant disorders classified as tissue dysplasias) and hamartoma-dysplasia syndromes; solid childhood tumors frequently associated with congenital disorders (Wilms' tumor, neuroblastoma, or retinoblastoma); double and multiple primary tumors (including tumors in "cancer families"); and tumors related to immunologic defects and chromosomal abnormalities, whether constitutional or acquired. No single hypothesis on the cause and pathogenesis of cancer seems to apply to all disorders. It is concluded that multiple causes and pathways lead to the phenotype "cancer". In particular, the pathogenic relationship between tissue dysplasias and cancers should be investigated further. (100 refs)

- 79-6638 **Respiratory System Differences Relevant to Lung Carcinogenesis Between Syrian Hamsters and Other Species.** (Eng) Kennedy, A. R. (Harvard Sch. Public Health, Boston, MA 02115); Little, J. B. *Prog Exp Tumor Res* 24: 302-314; 1979.

Features of the hamster respiratory system relevant to carcinogenesis and anatomic differences affecting carcinogenesis among species (including hamsters, dogs, rats, and humans) are discussed. Histologically, the hamster trachea is similar to the human bronchus; it includes cartilage, glands, lymph nodes, nodules, and an epithelium containing goblet, ciliated, basal, intermediate, and brush cells, but rarely contains neurosecretory cells. Carcinogen-induced tumors of the hamster tracheobronchial epithelium are histologically similar to human bronchogenic carcinomas. Major differences existing in the nature of the mucous ciliary escalator among species may alter the incidence and location of the tumors. It is suggested that differences in respiratory system structure, distribution of lymphoid tissues and glands, patterns of mucus secretion, and types of epithelial cells may account for differences in susceptibility to carcinogenesis among species. (61 refs)

- 79-6639 **Mesothelioma and Exposure to Mixtures of Chrysotile and Amphibole Asbestos.** (Eng) Acheson, E. D. (Southampton General Hosp., Southampton, England); Gardner, M. J. *Arch Environ Health* 34(4): 240-242; 1979.

Data indicating a possible synergistic interaction between chrysotile and amphiboles in the etiology of mesothelioma are reviewed. Mixtures of amphiboles and chrysotile have been found to occur much more commonly in the lungs of mesothelioma patients relative to controls than have either of the main types of fiber alone. Exposure to mixtures of amphiboles and chrysotile are associated with a relative risk of mesothelioma of 61, compared with a relative risk of 12 for amphiboles alone and 6 for chrysotile alone. The observed relative risk associated with exposure to fiber mixtures is closer to that expected based on a hypothesis of multiplicative interaction than on a simple additive effect hypothesis. Mixtures in which amphiboles are predominant may be associated with a higher relative risk of mesothelioma than those in which chrysotile is predominant. Mesothelioma is rarely a consequence of exposure to chrysotile or amosite alone, but occurs more frequently in persons exposed in or near crocidolite mines. Further work is needed to clarify these relationships. (16 refs)

- 79-6640 **Epidemiology of Oral and Pharyngeal Cancers in the United States: Review of Recent Literature.** (Eng)

Smith, E. M. (Dept. Epidemiology, SC-36, Sch. Public Health and Community Medicine, Univ. Washington, Seattle, WA 98195). *J Natl Cancer Inst* 63(5): 1189-1198; 1979.

Morbidity and mortality patterns, major etiologic factors, and social, demographic, cultural, or psychological variables related to oral cancer in the US are reviewed. Most oral neoplasms have been reported as squamous cell carcinomas. Lip tumors have the highest frequency and pharyngeal tumors the lowest frequency of localized neoplasms. The reverse is true for distant staging. No single site has been reported as having the highest incidence rate. Although lip cancer occurs with the greatest frequency, its incidence is high only among white males. Cancers of the tongue, floor of the mouth, and other mouth sites have the next highest frequency, but they show high incidence rates for all groups and are associated with poor survival. The major etiologic factors for oral cancer are tobacco and alcohol, and these effects are associated with age, sex, and religion, and ethnic backgrounds. Pharyngeal and gum-mouth sites are particularly vulnerable to alcohol, regardless of sex. In the synergistic relationship of tobacco and alcohol, the latter produces a slightly greater relative risk. Miscellaneous etiological factors include cirrhosis, syphilis, diabetes mellitus, dental conditions, and nutrition. Sociobehavioral factors associated with oral cancer include race, geographic location, religion as related to tobacco usage and alcohol consumption, and socioeconomic status. Sociobehavioral elements may alter risk, stage of disease at diagnosis, treatment, or survival from oral cancer. Further investigation is needed to determine the impact of these elements on the reduction of oral cancer incidence and mortality rates. (86 refs)

79-6641 Oral Cancer and Herpes Simplex Virus--A Review.
(Eng) Shillitoe, E. J. (Dept. Oral Medicine, Hosp. Dentistry Univ. California, San Francisco, CA 94143); Silverman, S. *Oral Surg* 48(3): 216-224; 1979.

Studies on an association between herpes simplex virus (HSV) and oral cancer are reviewed. In one study, eight patients who developed lip carcinoma at a site of previous frequent recurrent herpetic infection were described; however, these reports were anecdotal and have not been confirmed. Almost all investigators have found that women with cervical carcinoma have increased levels of HSV-2 antibody compared with matched control subjects. In one study, complement-fixing HSV-1 antibody levels in 24

oral cancer patients did not differ significantly from those in controls. In another experiment, virus was detected in only 1/31 cultures established from oral carcinoma specimens. Ultrastructural examination of 21 of these oral carcinomas failed to show virus particles. However, studies have shown that electron microscopy and tissue culture are inadequate methods for detecting DNA viruses. Antibody to an HSV-related antigen was demonstrated in 25/26 patients with oral cancer, compared with 3/51 normal subjects. This result was confirmed in a smaller series and also in patients with cervical cancer, but the tumor specificity of these reactions has not been properly established. Animal experiments have not yet demonstrated a direct carcinogenic effect of HSV in vivo, but a cocarcinogenic effect has been shown. There is fairly substantial evidence for an association between HSV-1 and oral carcinoma, but further studies with larger patient groups are needed to produce conclusive evidence. (62 refs)

79-6642 Welcome and Introduction: Evidence and Epidemiology of Ultraviolet-induced Cancers in Man.
(Eng) Urbach, F. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140). *Natl Cancer Inst Monogr* (50): 5-10; 1978.

Evidence is reviewed that supports the hypothesis that human skin cancer is causally related to chronic solar UV radiation exposure. The world distribution of UV radiation particularly the UV-B spectrum (280-320 nanometers), is discussed. There is a striking inverse relationship between nonmelanoma skin cancer incidence and latitude (linearly related to UV-B dose). The distribution of head and neck cancers is highest in skin areas receiving the most erythemogenic UV-B radiation. Melanin pigmentation is inversely associated with skin cancer: individuals with significant melanin pigmentation rarely develop skin cancer. Other variables in solar carcinogenesis include the time and duration of UV exposure, number of exposures per yr, clothing habits, occupation, age, genetic background, and environmental factors (wind, visible light, temperature, humidity, etc). The relationship of the thickness of the stratospheric ozone layer to the amount of solar UV-B that can reach the earth has been established. For each 1% reduction in ozone, there is approx a 2% increase in solar erythema-effective UV-B. Interactions between UV radiation and the increasing number of photoactive chemical agents in the environment are of growing concern. Whether a phototoxic agent will be photocarcinogenic or not remains to be determined. (13 refs)

CHEMICAL CARCINOGENESIS

- 79-6643 Effect of Intestinal Bacteria on Incidence of Liver Tumors in Gnotobiotic C3H/He Male Mice. (Eng) Mizutani, T. (Animal Physiology Lab., Wakohsi Inst. Physical and Chemical Res., Saitama 351, Japan); Mitsuoaka, T. *J Natl Cancer Inst* 63(6): 1365-1370; 1979.

The effect of intestinal bacteria on the incidence of liver tumors (ILT) was studied in germ-free (GF) male C3H/He mice, some of which were exposed to one or more pure cultures of bacteria. GF mice were kept in vinyl isolators and checked regularly for bacteria and fungi. Gnotobiotic (GB) mice were obtained from GF mice that were allowed to lick an appropriate culture broth; the first generation male offspring of these mice were used as the GB mice for the study. GB mice were also kept in vinyl isolators. Conventionalized mice (CN) were obtained by placing GF mice in aluminum cages in an ordinary animal facility. All mice were fed a commercial diet that was irradiated (5 millirads). They were autopsied at 18 wk of age. Among 49 GF mice, 19 (39%) had liver tumors; the number of tumor nodules/mouse (NTN/M) was 0.5. In the CN group, 14/17 (82%) had tumors, and the NTN/M was 1.6. All GB groups had liver tumor incidences >60%, except for GB12, in which 6/13 mice had liver tumors. This group was exposed to *Escherichia coli*, *Streptococcus fecalis*, *Lactobacillus acidophilus*, *Clostridium perfringens*, and *Bacteroides fragilis*. GB12 was the only group exposed to *L. acidophilus*. Monocontamination of this mouse strain with *L. acidophilus* was not achieved. The highest incidences were 12/12 among mice exposed to *Bacteroides multacidus*, and 19/20 among mice exposed to *E. coli*, *S. fecalis*, and four strains of *C. paraputrificum*. The latter group had the highest NTN/M observed (2.9). The histopathology was similar among the GF, GB, and CN groups. The tumor nodules observed did not invade the surrounding liver, and no metastases were found. No other types of neoplasms were observed. Most intestinal bacteria tested appeared to promote liver tumorigenesis. Bacterial interactions may also influence tumor incidence. (24 refs)

- 79-6644 Skin Cancer and Arsenical Intoxication from Well Water. (Eng) Wagner, S. L. (Environmental Health Sciences Center, Oregon State Univ., Corvallis, OR 97331); Maliner, J. S.; Morton, W. E.; Braman, R. S. *Arch Dermatol* 115(10): 1205-1207; 1979.

The occurrence of recurrent multiple clusters of arsenical keratoses and skin carcinomas in a 41-yr-old patient who had suffered arsenical intoxication 12 yr earlier is reported. Arsenical intoxication followed the ingestion of well water containing an extremely low level of arsenic (1.2 ppm). During the period from 12 to 15 yr following this episode, 43 skin lesions were removed. These lesions were shown histologically to be of two types: in situ squamous cell carcinomas of the arsenical type and superficial multicentric basal cell carcinomas without vacuolization. Arsenic was present in low levels in skin biopsy specimens from the normal-appearing back skin and from an area of skin cancer. This case supports the hypothesis that arsenic can be a carcinogen. (27 refs)

- 79-6645 Distribution of Cadmium in Human Blood Cultured in Low Levels of CdCl₂: Accumulation of Cd in Lymphocytes and Preferential Binding to Metallothionein. (Eng) Hildebrand, C. E. (Cellular and Molecular Biology Group, Univ. California, Los Alamos, NM 87545); Cram, L. S. *Proc Soc Exp Biol Med* 161(4): 438-443; 1979.

Cadmium metabolism in normal adult human blood exposed in culture to Cd at levels comparable to those found in the blood of humans exposed occupationally to this element was studied. Exposure of blood cells to CdCl₂ in culture resulted in Cd uptake by the lymphocytes, which accumulated approx 800-fold more Cd than did RBCs on a per cell basis. During the 72-hr exposure period, there was no evidence of cell death, and the blood cells did not clump. In lymphocyte lysates, approx 4% of the total cellular Cd was associated with the nuclear fraction. In RBCs, Cd was bound to several macromolecular species, none of which corresponded to the specific, inducible, Cd-binding protein metallothionein. In contrast, most Cd in the lymphocytes was associated with a low-mol-wt macromolecule characteristic of Cd-thionein. Cd exposure may alter normal immunocompetence associated with lymphocytes. (30 refs)

- 79-6646 Chromosomal Aberrations in Bone-Marrow Cells of Mice Given a Normal or a Calcium-deficient Diet Supplemented with Various Heavy Metals. (Eng) Deknadt, G. (Dept. Radiobiology, Mammalian Genetics Lab., B-2400 Mol, Belgium); Gerber, G. B. *Mutat Res* 68(2): 163-168; 1979.

Male C57Bl mice kept on a normal or low-calcium diet (1.1% and 0.03% Ca, respectively) were exposed for 1 mo to zinc chloride (0.5% Zn), lead acetate (0.5% Pb), or cadmium chloride (0.06% Cd) or to a mixture of these salts at half the above concentrations. Given in a poor calcium diet, these concentrations represent an LD₅₀/30 days. After the mice were killed, bone-marrow cells were assayed for chromosomal aberrations; and serum calcium was determined. Chromosomal aberrations were detected in the mice maintained on a low-calcium diet and exposed to lead, zinc or a mixture of lead, zinc and cadmium. The possible mechanism for the synergistic action on genetic effects of the lack of calcium and intoxication by heavy metals is discussed. (41 refs)

- 79-6647 Calcium Cyanamide. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (163): 1-112; 1979.

The carcinogenicity of calcium cyanamide was tested in 6-wk-old F344 rats and B6C3F1 mice. In subchronic studies with rats, calcium cyanamide caused diffuse follicular hyperplasia of the thyroid, which was dose related over the range 600 to 4,000 ppm. Preneoplastic changes were induced by the high dose. In chronic studies, male rats were fed calcium cyanamide at 100 or 200 ppm and females at 100 or 400 ppm for 107 wk; male and female mice received 500 or 2,000 ppm of the test chemical. In these studies, no

neoplasms could be clearly associated with calcium cyanamide administration in the rats, although the incidence of adrenal medullary tumors appeared to be in excess in the experimental groups based on the histopathologic examination. In male mice, the incidence of hemangiosarcoma was dose-related; in direct comparisons, however, incidences in the individual experimental groups were not significantly higher than those in controls (controls 1/20, low-dose 2/50, high-dose 10/50). In female mice, the incidences of lymphomas and leukemias were dose-related; in a direct comparison, the incidence of these tumors in the group that received the high dose was significantly higher than that in controls (controls 1/20, low-dose 11/46, high-dose 18/50). The incidence of these tumors in a historical-control group was 67/324, suggesting that the incidence of these tumors in the matched-control group in this study may have been abnormally low. Thus, neither the incidence of hemangiosarcoma in male mice nor of lymphomas or leukemias in female mice can clearly be related to calcium cyanamide administration. (19 refs)

- 79-6648 Bioassay of Lead Dimethyldithiocarbamate for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (151): 98 pp.; 1979.

A bioassay of technical grade lead dimethyldithiocarbamate was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice, at 25 or 50 ppm for 104-105 wk. Fifty rats or mice of each sex were used, and groups of 20 animals served as matched controls. Mean body wts of treated male rats and female mice were slightly lower than those of matched controls. Survival rates in both rats and mice were not altered by treatment, and the incidence of tumors was the same in treated and control animals. It is concluded that, under the conditions of the assay, lead dimethyldithiocarbamate is not carcinogenic for either Fischer 344 rats or B6C3F1 mice of either sex. (16 refs)

- 79-6649 High Incidence of Rat Mammary Carcinoma by Oral Administration of Ethyl Methanesulphonate. (Eng) Ueo, H. (First Dept. Surgery, Kyushu Univ., Fukuoka 812, Japan); Takaki, R.; Yamagami, H.; Nakano, S.; Okeda, T.; Sakakibara, K. *Cancer Lett* 7(2/3): 79-84; 1979.

The carcinogenicity of ethyl methanesulphonate (EMS) was tested in 40 female Wistar King A rats given 10^{-3} M in the drinking water for 12 wk. The rats were observed an additional 20 wk for tumor induction. Tumors were first detected 16 wk after the start of the study (6/40 rats) and gradually increased in number until the 32nd wk, when all 34 survivors had multiple sc tumors of various sizes in the neck and in the axillar and inguinal areas corresponding to bilateral mammary glands. There were no tumors in a control group. Histologically, the tumors were moderately differentiated adenocarcinomas of the medullary type. Most carcinomas showed invasive growth into the muscle layer or dermis and marked intraductal spread. Neither regional lymph node involvement nor distant metastases were detected. These histological findings and the sites of the tumors strongly suggest their mammary duct origin. (3 refs)

- 79-6650 HLA-B18 Antigens and Protection from Pulmonary Fibrosis in Asbestos Workers. (Eng) Huuskonen, M.

S. (Dept. Occupational Medicine, Inst. Occupational Health, Helsinki, Finland); Tiilikainen, A.; Alanko, K. *Br J Dis Chest* 73(3): 253-259; 1979.

The prevalence of histocompatibility locus (HLA) antigens was determined in Finnish asbestos workers with and without radiographic pulmonary fibrosis and in blood donors who had not been exposed to asbestos dust. Thirty-three HLA antigens were identified in a two-stage lymphocytotoxicity test with freshly separated peripheral lymphocytes from 64 patients with asbestosis and from 37 matched control subjects. The antigen frequencies of these groups were compared with those of 900 blood donors. The prevalence of HLA-B18 was decreased in the asbestosis subjects compared with the other groups. In the 37 exposed control subjects, the prevalence of HLA-B27 and Cw2 was increased. Lung cancers were found in six asbestosis subjects, all cigarette smokers. There were no significant differences in the HLA antigens between these patients and other workers with asbestosis or the blood donors. No association was detected between any HLA antigen and the severity of asbestosis, or the progression of diffuse fibrosis. No HLA antigen was correlated with the rate at which pulmonary fibrosis developed during exposure to asbestos. However, the increase in HLA-B27, Cw2, and HLA-B18 in the asbestos-exposed controls suggests that these antigens may protect against the development of pulmonary diffuse fibrosis. (9 refs)

- 79-6651 Effect of Methylmercury Chloride on Transplacental Tumors Induced by Sodium Nitrite and Ethylurea in Rats. (Eng) Nixon, J. E. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR 97331); Koller, L. D.; Exon, J. H. *J Natl Cancer Inst* 63(4): 1057-1063; 1979.

The effect of methylmercury chloride (MeHg; 10 ppm in diet from weaning through mating and pregnancy until delivery) on the induction of transplacental tumors by sodium nitrite (SN; 0.5-2.0 g/liter in drinking water or 25-50 mg/kg by gavage during pregnancy) plus ethylurea (EU; 0.159%-0.63% of the diet or 50-100 mg/kg by gavage during pregnancy) was studied in W rats. Compared with controls (SN-EU only), the survival times of the postweanling progeny of rats given MeHg plus the two highest doses of SN-EU were reduced by 49% and 43%, respectively. These animals also developed tumors after mean latency periods 45% and 28% shorter, respectively, than those of the controls. Rats from the dams given MeHg plus the highest dose of SN-EU showed a 67% incidence of neural tumors before the first such tumor appeared in controls. The minimum latency period for the induction of neural tumors was reduced by 5 wk in the group given MeHg. The incidence of cranial nerve schwannomas was higher in the progeny of rats given MeHg plus SN-EU than in the SN-EU controls, and ependymomas appeared only in the progeny of the MeHg-treated dams. MeHg did not appear to affect the incidence or latency of neural tumors in the progeny of rats given the lowest doses of SN-EU. (24 refs)

- 79-6652 Mutagenicity of Metal Cations in Cultured Cells from Chinese Hamster. (Eng) Miyaki, M. (Dept. Biochemistry, Tokyo Metropolitan Inst. Medical Science, 3-18, Honkomagone, Bunkyo-ku, Tokyo 113, Japan); Akamatsu, N.; Ono, T.; Koyama, H. *Mutat Res* 68(3): 259-263; 1979.

The mutagenicity of metal chlorides (BeCl_2 , MnCl_2 , CoCl_2 , and NiCl_2) on cultured V79 Chinese hamster cells at the hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) locus was

evaluated using the technique of selection for resistance to 8-azaguanine (8-AG). The spontaneous mutant frequency of 8AG resistance was $5.8 \pm 0.8/10^6$ cells. Treatment with BeCl_2 (2-3 mM) or MnCl_2 (1-1.5 mM) increased the resistance 2- to 6-fold. Approx 75% of the 8AG-resistant colonies were sensitive to amethopterin and 86% of the resistant colonies showed less than 3% of the wild-type HGPRTase activity. The mutant frequency of cells treated with CoCl_2 (0.2 mM) and NiCl_2 (0.4-0.8 mM) was only moderately increased (1.2- to 2.7-fold) and detectable only at low rates of cell survival. (14 refs)

- 79-6653 Cylindrical Laminated Bodies in Nickel-Subsulphide-induced Rhabdomyosarcoma in Rabbits. (Eng) Hildebrand, H. F. (Institut de Recherches sur le Cancer de Lille, Unite 124 de l'INSERM, B.P. no 3567, F-59020 Lille Cedex, France); Biserte, G. *Eur J Cell Biol* 19(3): 276-280; 1979.

Rabbit rhabdomyosarcoma was induced by im implantation of a large quantity of very pure nickel subsulphide. Until the present time, the rabbit has been considered resistant to Ni_3S_2 tumorigenesis. The tumors were similar to those induced in rats under the same conditions. Four different cell types were observed: small polygonal cells, small elongated cells, giant cells, and mature myofibers. Electron microscopy revealed a complete disorientation of myofibrils in mature myoblasts. Giant cells appeared by pluripolar endomitosis and always contained myofibrillar structures, but M-lines and Z-lines were not present in these cells. Cylindrical laminated bodies were observed very often in all four cell types. They were formed of 4-nanomole fibrils arranged in crossed position in each lamella. Some of these paracrystalline structures were also observed in nuclei. The laminated bodies were considered to be abnormal formations of contractile proteins produced during tumoral myofibrillar differentiation. (24 refs)

- 79-6654 Fenthion. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (103): 1-104; 1979.

The carcinogenicity of the organophosphate pesticide fenthion (10 or 20 ppm in the diet for 103 wk) in F344 rats and B6C3F1 mice was studied. There was no evidence of appreciable toxicity in either species during the study, although the survival of male mice given 10 ppm fenthion was significantly reduced relative to that in control mice. The incidence of interstitial cell tumors of the testes was nonsignificantly increased in male rats relative to that in untreated control rats. No significant increase in tumor incidence occurred in fenthion-treated female rats or mice relative to untreated controls. Dose-related increases in the incidence of sarcomas, fibrosarcomas, and rhabdomyosarcomas of the integumentary system were observed in fenthion-treated male mice relative to untreated controls. Although the data did not meet the Bonferroni criterion of significance, it is concluded that these tumors were associated with the administration of the pesticide. The data indicate that under the conditions of this bioassay, fenthion is not carcinogenic in F344 rats or female B6C3F1 mice, but that it may be carcinogenic in B6C3F1 mice. (21 refs)

- 79-6655 Bioassay of Phosphamidon for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention,

NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (16): 98 pp.; 1979.

The carcinogenicity of technical grade phosphamidon (PA, 80 or 160 ppm, incorporated in the feed for 62-80 wk) was studied in Osborne-Mendel rats and B6C3F1 mice. Indications of PA toxicity were observed in both species, but sufficient numbers of animals lived long enough to be at risk for the development of late-appearing tumors. The incidence of hemangiomas and hemangiosarcomas of the spleen in the PA-treated male rats showed a significant increase with dose, but the incidence was not significantly higher than in matched controls or historical controls from the same laboratory. The incidence of C-cell adenomas and carcinomas of the thyroid was significantly increased in a dose-dependent fashion in the PA-treated female rats, but the incidence was not significantly higher than in historical controls from the same laboratory. Tumor incidence in the PA-treated mice was not significantly increased. It was concluded that under the conditions of this bioassay, PA is not carcinogenic for B6C3F1 mice. The data were insufficient to allow conclusions regarding the carcinogenicity of PA for Osborne-Mendel rats. (14 refs)

- 79-6656 Bioassay of Formulated Fenaminosulf for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Tech Rep Ser* (101): 50 pp.; 1979.

The carcinogenicity of the fungicide fenaminosulf [p-(dimethylamino)benzenediazosulfonic acid sodium salt] was tested in Fischer 344 rats and B6C3F1 mice divided into groups of 50 animals of each sex. Fenaminosulf was administered in the feed at concentrations of 0.10% and 0.05% for rats, 0.19% and 0.10% for male mice, and 0.10% and 10.05% for female mice. Control animals in corresponding numbers were fed a basal diet. After receiving the compound for 78 wk, the rats were observed for an additional 31 wk and the mice for an additional 19 wk. Tissue masses were determined by monthly observation and palpation. Necropsies were performed on all animals whether they died naturally or were sacrificed. Slides were prepared from 30 separate organs or tissues. There was a significant association between fenaminosulf dosage and mortality among mice. Rats did not show such an association. In neither species was there a significant association between chemical administration and the incidence of neoplasms. Endometrial stromal sarcomas were found in treated female rats, but their incidence was not significantly higher than that in control rats. An increased incidence of necrosis and mineralization of the renal papillary tubules occurred in treated animals of both species, compared with controls. It is concluded that under the conditions of this bioassay, dietary fenaminosulf was not carcinogenic in either rats or mice. (18 refs)

- 79-6657 Trauma, High-Molecular-Weight Dextran, and Tumor Growth. (Spa) Agostino, D. (Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY 10032); Agostino, N. *Sangre (Barc)* 24(5): 504-512; 1979.

The effects of high-mol-wt dextran (HMD, mean mol wt 1,000,000, 0.15 g/100 g in saline soln) on trauma induced by the im injection of turpentine (0.2 ml) into the right leg, and of the combination of HMD and trauma on the frequency of pulmonary metastases were studied in 400 female adult Wistar rats with

Walker's carcinosarcoma 256. Tumor cells were injected into the femoral vein 10 min after HMD and 48 hr after the injection of turpentine. The frequency of pulmonary metastases was 32% in the control group treated with tumor cells only, 48% in the group treated with HMD, 51% in the traumatized group, and 69% in the group treated with both HMD and turpentine. Both HMD and trauma caused a significant increase in the frequency of pulmonary metastases ($p < 0.001$). No definite explanation of the combined effect of trauma and HMD can be offered at present. (32 refs)

79-6658 Bioassay of Ethyl Tellurac for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (152): 112 pp.; 1979.

Ethyl tellurac was tested for possible carcinogenicity in F344 rats and B6C3F1 mice. Groups of 50 rats of each sex were fed a diet containing the test chemical at one of two doses (300 or 600 ppm for males, 150 or 300 ppm for females) for 105 wk; groups of 20 animals fed a normal diet were used as controls. Groups of 50 mice were fed a diet initially containing 2,500 or 5,000 ppm. Because of signs of toxicity, the doses were reduced to 500 and 2,000 ppm at wk 38 (females) or wk 41 (males); the reduced doses were maintained for 66 wk for the males and raised to 2,000 and 5,000 ppm after 3 wk for the females. Mean body wts of treated animals were lower than those of control animals throughout the assay. Mortality was unaffected by treatment. An increased incidence of mesotheliomas occurred in male rats; this increased incidence was dose-related but not statistically significant. Adenomas of the lacrimal gland of the eye were observed in treated mice of both sexes but not in untreated animals; the increased incidence was not statistically significant. It is concluded that, under the conditions of the assay, ethyl tellurac was not carcinogenic in F344 rats and B6C3F1 mice. (20 refs)

79-6659 Bioassay of Iodoform for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (110): 44 pp.; 1978.

The possible carcinogenicity of technical-grade iodoform (triiodomethane) was tested by administering it to Osborne-Mendel rats and B6C3F1 mice for 78 wk. Groups of 50 mice or rats of each sex received iodoform by gavage in one of two dosages (142 and 71 mg/kg/day for male rats, 55 and 27 mg/kg/day for female rats, 93 and 47 mg/kg/day for both male and female mice). The treatment period was followed by an observation period of 34 wk for rats and 13-14 wk for mice. Groups of 20 matched animals similarly gavaged with pure corn oil or only fed a normal diet were used as vehicle and untreated controls. A correlation between dose and mortality was observed in male rats and mice of both sexes. No statistically significant differences in tumor incidence between treated animals and their matched controls was observed. It is concluded that, under the conditions of the assay, iodoform is not carcinogenic for Osborne-Mendel rats or B6C3F1 mice of either sex. (23 refs)

79-6660 Bioassay of dl-Menthol for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH,

Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (98): 112 pp.; 1979.

The carcinogenicity of dl-menthol (3,750 or 7,500 ppm for rats and 2,000 or 4,000 ppm for mice, incorporated in the diet for 103 wk) for Fischer 344 rats and B6C3F1 mice was studied. Although a dose-related increase in mortality was observed in the menthol-treated female mice, survival at the end of the study was at least 62% in all groups. In neither of the species tested was tumor incidence in the menthol-treated animals significantly greater than that in the matched controls. Thus, under the conditions of this bioassay, dl-menthol was not carcinogenic for B6C3F1 mice or Fischer 344 rats. (28 refs)

79-6661 Induction of Chromosomal Aberrations in Peripheral Lymphocytes of Human Blood in Vitro, and of SCEs in Bone Marrow Cells of Mice in Vivo by Ethanol and Its Metabolite Acetaldehyde. (Eng) Obe, G. (Genetics Inst., Free Univ., Berlin, W. Germany); Natarajan, A. T.; Meyers, M.; den Hertog, A. *Mutat Res* 68(3): 291-294; 1979.

The chromosome breaking activity of acetaldehyde in cultured human lymphocytes from three healthy individuals and one patient with Fanconi's anemia and the effect of long term consumption of ethanol or treatment with acetaldehyde on the incidence of sister chromatid exchange (SCE) in mouse bone marrow cells were investigated. Acetaldehyde (0.001 or 0.002%, v/v) had no chromosome-breaking activity in lymphocytes from healthy individuals but induced a large number of chromatid-type aberrations in lymphocytes from the patient with Fanconi's anemia. Groups of 2-6 mice received either ethanol or tap water as their only liquid supply; then after 3, 5, 12, or 16 wk, they received a sc implantation of 55 mg 5-bromodeoxyuridine (BrdU) followed at 24 hr by an ip injection of colcemide. In another experiment, mice received ip injections (1 or 0.5 ml) of $10^{-4}\%$ (v/v) acetaldehyde soln followed by the BrdU and colcemide treatment. Routine preparations of bone marrow cell chromosomes were made and scored for SCE. A marked elevation of SCE was observed in the mice that drank only ethanol and in those injected with acetaldehyde. These data support the hypothesis that alcohol is carcinogenic in man. (13 refs)

79-6662 Mutagenic and Carcinogenic Effects of Vinyl Chloride. (Cze) Kucerova, M. (Katedra pediatrie, Institut pro dalsi vzdelavani lekaru a farmaceutu, Budejovicka 800, Prague 4, Czechoslovakia); Polivkova, Z.; Batora, J. *Prac Lek* 31(6/7): 249-252; 1979.

The mutagenicity of vinyl chloride (VC) was studied in peripheral blood lymphocytes of nine workers at a polyvinyl chloride manufacturing plant. The workers have been exposed to VC at concentrations of 15-150 ppm for 10-25 yr. Two of three cytogenetic examinations performed over a 2-yr period did not reveal any significant increase in the percentage of cells with chromosome aberrations compared with that in eight nonexposed controls; the final test, however, showed a significant increase in the percentage of cells with chromosome aberrations in three workers (5.2% vs 1.8% in the controls). The sister chromatid exchange (SCE) test was also performed at the time of the third test: it demonstrated significant increases in SCE frequency in 5/7 tested workers (13.8% vs 9.41% in the controls). (23 refs)

79-6663 Dermatological Aspects of so Called Vinyl Chloride Monomer Disease. (Eng) Czernielewski, A. (Dermatological Clinic, Medical Acad., Krzemieniecka 5, Lodz, Poland); Kiec-Swierczynska, M.; Gluszczyk, M.; Wozniak, L. *Derm Beruf Umwelt* 27(4): 108-112; 1979.

Dermatological findings in 30 workers (aged 26-54 yr) who had been in close and continuous contact with various phases of the vinyl chloride (VC) polymerization process for 2-11 yr are presented. The most common abnormalities were histopathologic changes (30 workers); history of symptoms of Raynaud's phenomenon (25 workers); positive results in digital plethysmography (24 workers) and in the vibro-tactile threshold sensory test (24 workers); and scleroderma-like skin lesions (23 workers). Acro-osteolysis was found in three patients and thrombocytopenia in one. Most abnormalities disappeared or showed signs of healing within 1-2 yr after exposure was discontinued. These results indicate the importance of dermatological examination in detecting the clinical pattern of VC-induced disease. (32 refs)

79-6664 Interaction of Potential Metabolites of the Carcinogen Ethylene Dibromide with Protein and DNA in Vitro. (Eng) Banerjee, S. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY 10016); Van Duuren, B. L.; Kline, S. A. *Biochem Biophys Res Commun* 90(4): 1214-1220; 1979.

The covalent binding of ethylene dibromide (EDB), bromoacetaldehyde, and 2-bromoethanol to macromolecules was determined. [14 C]-bromoacetaldehyde and [14 C]-2-bromoethanol were synthesized from [14 C]-paraldehyde and [14 C]-ethylene oxide, respectively. EDB bound covalently to protein and DNA in a microsomal system prepared from male B6C3F1 mouse liver. Bromoacetaldehyde and 2-bromoethanol bound without enzymatic activation. Under these conditions, bromoacetaldehyde bound faster to macromolecules than did EDB or 2-bromoethanol. 2-Bromoethanol bound faster to DNA than did EDB but slower to protein. Both bromoacetaldehyde and 2-bromoethanol bound to protein and DNA to a greater extent than did EDB. These findings suggest that bromoacetaldehyde and 2-bromoethanol are important intermediates in EDB carcinogenesis. (16 refs)

79-6665 1,1-Dichloro-2,2-bis(p-ethylphenyl) ethane. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (156): 1-115; 1979.

The carcinogenicity of the pesticide 1,1-dichloro-2,2-bis(p-ethylphenyl)ethane (p,p'-E-DDD) was studied in F344 rats and B6C3F1 mice. The compound was incorporated in the diet for 105 wk, at 3,500 or 7,000 ppm in rats, 2,500 or 5,000 ppm in male mice, and 5,000 or 10,000 ppm in female mice. Subchronic feeding studies were conducted to determine the max tolerated doses of p,p'-E-DDD. Dose-dependent decreases in mean body wt were observed in experimental mice and rats, but mortality was unaffected by pesticide treatment. Tumor incidences in pesticide-treated rats and male mice were similar to control incidences in these species. Dose-related increases in the incidences of hepatocellular carcinomas and adenomas were observed in p,p'-E-DDD-treated female mice compared with controls. Although the increase was not statistically significant, it is suggested that these tumors may have been related to administration of the test chemical. Hepatocellular tumors were previously found

to occur following administration of p,p'-E-DDD and related compounds. It is concluded that under the conditions of this bioassay, p,p'-E-DDD is not carcinogenic for F344 rats or for male B6C3F1 mice, but that it may be carcinogenic in female B6C3F1 mice. (25 refs)

79-6666 Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice. (Eng) Van Duuren, B. L. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY 10016); Goldschmidt, B. M.; Loewengart, G.; Smith, A. C.; Melchionne, S.; Seidman, I.; Roth, D. *J Natl Cancer Inst* 63(6): 1433-1439; 1979.

Fifteen halogenated hydrocarbons of industrial and environmental importance were tested for carcinogenicity following chronic administration to Ha:1CR Swiss mice. Allyl chloride, 1,2-dibromo-3-chloropropane (DBCP), and vinylidene chloride initiated skin tumors when phorbol myristate acetate was used as a promoter. 1,2-Dibromoethane (DCE) was the only compound that significantly increased the incidence of skin papillomas, skin carcinomas, and lung tumors following repeated topical applications ($p < 0.05$). DCE, DBCP, and 1,1,2,2-tetrabromoethane induced lung and/or stomach tumors after repeated topical applications. cis-1,3-dichloro-propene and 2-chloropropanol induced sarcomas following sc administration, and stomach tumors developed following administration of 1-chloropropane by intragastric intubation. The following compounds showed no carcinogenic properties in this study: trichloroethylene, tetrachloroethylene, hexachlorobutadiene, chloroacetaldehyde, cis-1-chloropropene oxide, (trans-1-chloropropene oxide), and trichloroethylene oxide. (31 refs)

79-6667 Inhibition of Mammary Carcinogenesis of Dimethylbenzanthracene Treated Rats with a Brominated Triphenylethylene. (Eng) Rudali, G. (Equipe de Recherches 190 du C.N.R.S., Fondation Curie, 26, rue d'Ulm, 75231 Paris Cedex 05, France); Montes-Rendon, A.; Assa, R. *Biomedicine [Express]* 31(5): 142-146; 1979.

The effect of a brominated triphenylethylene (TBP, 2 or 20 ppm in the diet) on dimethylbenz(a)anthracene (DMBA, 20 mg po)-induced mammary carcinogenesis was studied using female Sprague-Dawley rats. All animals given DMBA alone developed tumors with a mean latency of 61 days. Rats given 2 ppm TBP plus DMBA had a 60% incidence of tumors after a mean latency of 82 days. In rats given 20 ppm TBP plus DMBA, the tumor incidence was 33-41% after a 4- to 5-mo latency period. The wt of the ovaries was greater in rats given DMBA only than in those given DMBA plus TBP, and TBP administration prevented the appearance of corpora lutea in the ovaries. The weights of the other glands were similar in rats given TBP plus DMBA or DMBA alone, and TBP did not prevent the necrosis of the adrenal cortex induced by DMBA. The mammary tumors were all adenocarcinomas, usually papillary with cysts and acini, except for one adenofibroma. The data suggest that TBP probably inhibits tumor development at an early stage. (20 refs)

79-6668 Induction of Unscheduled DNA Synthesis in Mouse Germ Cells Following 1,2-Dibromo-3-Chloropropane

(DBCP) Exposure. (Eng) Lee, I. P. (Lab. Environmental Toxicology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Suzuki, K. *Mutat Res* 68(2): 169-173; 1979.

Acute toxicity studies of 1,2-dibromo-3-chloropropane (DBCP) were carried out in CD-1 male mice, and the effect of DBCP on germ cell DNA was investigated. The toxicity studies demonstrated that the respective LD₅₀ values for prepubertal and adult mice were 180.7 mg/kg (154.0-197.5 mg/kg body wt) and 123 mg/kg (100.5-141.5 mg/kg body wt), which were significantly different. The slopes of the dose response curves (1.2) were steep and essentially the same, indicating a narrow margin of safety. In prepubertal male mice, a single maximally tolerated dose of DBCP (100 mg/kg, ip) induced significant unscheduled DNA synthesis in the premeiotic germ cells but not in spermatozoa. The authors speculate that dehydrobromination of DBCP molecules may result in a reactive aliphatic epoxide; which would then react with cellular macromolecules. Male sterility induced by chronic DBCP exposure may be attributed to saturation of germ cell DNA-repair capacity and thus, consequent manifestation of germinal aplasia in humans. (19 refs)

79-6669 Bioassay of Allyl Chloride for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (73): 53 pp.; 1979.

The carcinogenicity of technical grade allyl chloride (AC, 57 or 77 mg/kg/day for male rats, 55 or 73 mg/kg/day for female rats, 172 or 199 mg/kg/day for male mice, and 129 or 258 mg/kg/day for female mice, given by gavage 5 days/wk for 78 wk), a widely-used chemical intermediate, was studied in Osborne-Mendel rats and B6C3F1 mice. Survival of rats and male mice given the highest doses of AC was extremely poor, so that the number of animals surviving long enough to be at risk from late-developing tumors was not adequate for meaningful statistical analysis. The incidences of squamous cell carcinomas of the forestomach in AC-treated male and female mice and squamous cell papillomas of the forestomach in AC-treated female mice were higher than in historical controls from the same laboratory. Thus, 0.0, though no convincing evidence was obtained for the carcinogenicity of AC in Osborne-Mendel rats, the results suggest that this compound may be carcinogenic for B6C3F1 mice. (18 refs)

79-6670 Carcinogen-induced Chromosome Breakage in Chromosome Instability Syndromes. (Eng) Auerbach, A. D. (Lab. Genetics, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Wolman, S. R. *Cancer Genet Cytogenet* 1(1): 21-28; 1979.

Cultured fibroblasts from patients with chromosome instability syndromes [Fanconi's anemia (FA), ataxia telangiectasia (AT), Bloom's syndrome (BS), xeroderma pigmentosum (XP)] and from normal individuals were examined for their susceptibility to diepoxybutane (DEB)-induced chromosome breakage. Clear differences in patterns of spontaneous and induced chromosome breakage in the different syndromes were found. In FA and AT, chronic exposure to a low concentration of the carcinogen induced extensive chromosome damage without reduction in cell viability. Exposure to the same concentration of carcinogen had no clastogenic effect on BS, XP, or normal fibroblasts. Furthermore,

when normal fibroblasts were exposed to a higher dose of the same chemical, there was a significant reduction in viability with little increase in chromosome aberrations. These experiments separate the clastogenic effect of DEB from its cytotoxic effect, and show genetic differences in susceptibility of cells to carcinogen-induced chromosome damage. (30 refs)

79-6671 On the Mutagenicity of Methadone Hydrochloride. Induced Dominant Lethal Mutation and Spermatocyte Chromosomal Aberrations in Treated Males. (Eng) Badr, F. M. (Dept. Zoology, Faculty Science, Univ. Kuwait, P.O.B. 5969, Kuwait); Rabouh, S. A.; Badr, R. S. *Mutat Res* 68(3): 235-249; 1979.

Inbred male C3H mice were treated ip with methadone hydrochloride (METH: 1-6 mg/kg/day x 3) before mating to virgin females for a total of 45 days. All METH doses increased the rate of preimplantation deaths in all postmeiotic stages. The higher doses (4-6 mg/kg) also affected spermatogonia. A quantitative dose-effect relationship could not be demonstrated, but the spectrum of changes increased with higher doses as more stages of spermatogenesis became more sensitive to METH. Mutation indices (based on total embryonic deaths) showed that METH affected spermatozoa, early and late spermatids, late spermatocytes, and spermatogonial stages. Chromosome analysis at diakinesis-metaphase I disclosed significant increases in the frequencies of sex chromosome and autosome univalents at all METH doses. A direct dose-effect relationship was observed. The most frequent multivalent type was chain quadrivalents. Translocation frequencies increased in a dose-dependent fashion at the lowest doses (0.1-0.2 translocations/cell at 1-4 mg/kg) but declined abruptly (0.05/cell) at the highest dose (6 mg/kg). It is concluded that METH may pose a genetic hazard to human populations. (43 refs)

79-6672 Rapid Induction of Epithelial Hyperplasia and Lymphoplasmacytosis in the Chinese Hamster (*Cricetus griseus*) by Mineral and Pristane Oil. (Eng) Yerganian, G. (Inst. Environmental Biomedical Sciences, Northeastern Univ., 360 Huntington Ave., Boston, MA 02115); Paika, I.; Gagnon, H. J.; Battaglino, A. *Prog Exp Tumor Res* 24: 424-434; 1979.

The development of pleomorphic lesions and latent tumors in response to mineral oil and pristane oil in pancreatic tissue and epithelial tissues of various organs in nondiabetic Chinese hamsters was studied. One hundred and twenty-one animals (both sexes, 288-452 days old) were randomly assigned to experimental groups (including 62 in the control group). Animals were sacrificed monthly following an initial ip injection of 0.5 ml of oil; tissues (heart, lung, liver, spleen, pancreas, kidney, adrenal) were fixed in Tellyesniczky's soln, embedded in paraffin, and sectioned at 5 µm before staining with hematoxylin and eosin. Approx 50% of the treated animals developed vasculitis and lymphoplasmacytosis, and 40% developed adrenal medullary hyperplasia (with predominance of males) and renal tubular hyperplasia. Intravascular and intraductal sarcomatoid occlusions prevailed by the 30th day after treatment; these appeared as prominent whorls of aggregated epithelioid cells within the vessels and ducts of the pancreatic mesothelium and lobules. Three of 17 males treated with pristane oil developed sarcomatous pancreatic tumors 32-79 days after treatment; these lesions were associated with extramedullary hematopoiesis and adrenal medullary hyperplasia. Two of 27 females developed tumors (1 hepatocarcinoma 167 days after treatment, 1 pleomorphic tumor associated with ex-

tramedullary hematopoiesis and regenerating liver 67 days after treatment with mineral oil). The heightened sensitivity of the Chinese hamster pancreas to the development of oil-induced lesions is believed to reflect the (auto)immune response portion of the genotype previously associated with diabetes mellitus. (22 refs)

79-6673 Morphology and Morphogenesis of Experimentally Induced Small Intestinal Tumors. (Eng) Hohn, P. (Pathologisches Institut der Universität, Postfach 3960, Langenbeckstrasse 1, 6500 Mainz, W. Germany). *Curr Top Pathol* 67: 69-144; 1979.

The morphology and morphogenesis of experimentally induced small intestinal tumors were studied. Intestinal tumors appeared in 250 rats 90-200 days after the administration of 1,2-dimethylhydrazine (200-300 mg/kg total, sc). The site of predilection was the upper small intestine, and the first detectable change was the appearance of circumscribed mucosal hyperplasias. Expansion of the proliferative compartment was associated with goblet cell atrophy and loss of differentiation capacity in enterocyte precursors. Adenomas and well-differentiated adenocarcinomas developed in these centers of proliferation, and poorly differentiated adenocarcinomas and solid carcinomas appeared to arise directly from transformed basal crypt epithelium. The tumors showed a largely endophytic growth, and they rapidly infiltrated the deeper layers of the intestinal wall. Numerous characteristic structures of the crypt epithelium were demonstrated in the tumor cells, and scanning electron microscopy showed that the differentiation of certain structures decreased with decreasing degrees of tumor maturation. A slight differentiation of the apical cell membranes of the tumor cells compared with the brush borders of normal enterocytes was associated with markedly diminished development of the glycocalyx. With the exception of alkaline phosphatase, enzymes located mainly in the endoplasmic reticulum and brush border of the enterocytes were no longer demonstrable in the tumor cells. It is concluded that the morphogenesis and morphology of these tumors are largely identical to those of human intestinal adenomas and carcinomas. (134 refs)

79-6674 Selective Protective Effect of Butylated Hydroxytoluene Against 1,2-Dimethylhydrazine Carcinogenesis in BALB/c Mice. (Eng) Clapp, N. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Bowles, N. D.; Satterfield, L. C.; Klima, W. C. *J Natl Cancer Inst* 63(4): 1081-1087; 1979.

The effect of the antioxidant butylated hydroxytoluene (BHT) on 1,2-dimethylhydrazine (DMH)-induced carcinogenesis was studied in male and female BALB/c mice. Survival was increased in male ($p < 0.001$) and female ($p = 0.011$) mice treated with BHT (0.75% of the diet beginning at 8 wk of age and continuing for life) plus DMH (20 mg/kg, sc, for 10 wk beginning at 11 wk of age) compared with those given DMH alone. The development of adenomas and adenocarcinomas in the descending colon and rectum was decreased significantly ($p = 0.0036$) in males and non-significantly in females given BHT plus DMH compared with those given DMH alone. The number of tumors per tumor-bearing mouse was also reduced by BHT treatment in both sexes. Colon and rectal tumors did not develop in BHT-treated or -untreated controls given no DMH. DMH alone induced lung tumors, while BHT alone did not; DMH plus BHT induced fewer lung tumors than DMH alone. The sex-specific protective effect of BHT on the

survival of mice treated with DMH and on the development of large bowel tumors (males only) resembled the sex-specific effect of BHT on diethylnitrosamine-induced squamous cell tumors in the female forestomach, but the mechanisms remain unknown. (31 refs)

79-6675 Promotional Effect of Sodium Barbiturate on Intestinal Tumors Induced in Rats by Dimethylhydrazine. (Eng) Pollard, M. (Lobund Lab., Univ. Notre Dame, Notre Dame, IN 46556); Luckert, P. H. *J Natl Cancer Inst* 63(4): 1089-1092; 1979.

Noninbred Sprague-Dawley rats received 1,2-dimethylhydrazine hydrochloride (DMH) by gavage or methylazoxymethanol acetate sc. Thereafter, one group received water to which 0.1% sodium barbiturate was added, and the other was given drug-free water. They were examined 20 wk after the beginning of the experiments. A direct relationship was noted between DMH dose and numbers of intestinal tumors induced in the rats. Rats given sodium barbiturate developed more intestinal tumors than did controls. (26 refs)

79-6676 Bioassay of (2-chloroethyl)trimethylammonium chloride (CCC) for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (158): 104 pp.; 1979.

(2-Chloroethyl)trimethylammonium chloride was tested for possible carcinogenicity in F344 rats and B6C3F1 mice. Groups of 50 rats or mice of each sex were fed a diet containing the test chemical in either of two concentrations (1,500 or 3,000 ppm for rats; 500 or 2,000 ppm for mice) for 108 wk (rats) or 102 wk (mice). Groups of 20 matched controls fed a normal diet were used. Mean body wt of treated animals was lower than that of controls (except in male mice). No toxic signs or dose-related mortality were observed. No significant increase in tumor incidence was observed in treated animals. It is concluded that, (2-chloroethyl)trimethylammonium chloride is not carcinogenic for F344 rats or B6C3F1 mice of either sex, under the conditions of the assay. (17 refs)

79-6677 Results of a Two-Year Chronic Toxicity and Oncogenic Study of Rats Ingesting Diets Containing 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T). (Eng) Kociba, R. J. (Toxicology Res. Lab., Health and Environmental Res., Dow Chemical USA, Bldg. 1803, Midland, MI 48640); Keyes, D. G.; Lisowe, R. W.; Kalnins, R. P.; Dittenber, D. D.; Wade, C. E.; Gorzinski, S. J.; Mahle, N. H.; Schwetz, B. A. *Food Cosmet Toxicol* 17(3): 205-221; 1979.

Groups of Sprague-Dawley rats (50 males and 50 females) were maintained on diets supplying 3, 10 or 30 mg 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)/kg body wt/day for up to 2 yr, with an interim autopsy (on an additional 10 males and 10 females per group) after 118-119 days. The highest dose level was associated with some degree of toxicity, including a decrease in body wt gain and increases in relative kidney wt, in the volume of urine excreted and in the urinary excretion of coproporphyrin and uroporphyrin, plus slight morphological changes in the kidney, liver and lungs. The kidney changes primarily involved the presence of mineralized deposits in the renal pelvis. Parameters not adversely affected by this dose level included death rate, food

consumption, the occurrence of palpable masses, hematological indices, the results of routine urine analyses, urinary excretion of creatinine and delta-aminolevulinic acid, serum-chemistry values, wt of organs other than the kidneys, tumor incidence and gross and microscopic morphology of organ systems other than those mentioned above. At the intermediate dose level only minimal effects were noted, primarily an increased incidence of mineralized deposits in the renal pelvis and, in the males and only during the early phase of the study, an increase in urinary excretion of coproporphyrin. At the low dose level there were no changes that were considered to be related to treatment throughout the 2-yr period. Thus, this study revealed no oncogenic response in rats, even when the duration of 2,4,5-T administration extended over most of their life span at a dosage high enough to induce toxicity. (13 refs)

- 79-6678 Effects of Exposure to Acetaldehyde in Syrian Hamsters Simultaneously Treated with Benzo(a)pyrene or Diethylnitrosamine. (Eng) Feron, V. J. (Central Inst. Nutrition and Food Res. TNO, Zeist, Netherlands). *Prog Exp Tumor Res* 24: 162-176; 1979.

The chronic effects of acetaldehyde (AA, 1,500 ppm, 7 hr/day, 5 days/wk for 52 wk, administered as a vapor) and its possible significance as a cofactor in respiratory carcinogenesis induced by intratracheal benzo(a)pyrene (BP) or diethylnitrosamine (DENA) were studied using male Syrian golden hamsters. Exposure to AA vapor resulted in epithelial hyper- and metaplasia accompanied by inflammation of the nasal cavity and trachea. Extensive peribronchiolar adenomatoid lesions often accompanied by inflammatory changes occurred in the lungs after intratracheal instillations of AA (0.2 ml of a 4% soln given weekly). There was no evidence of a carcinogenic effect. Polyps, papillomas, squamous cell carcinomas, squamous adenocarcinomas, adenocarcinomas, fibrosarcomas, and/or anaplastic carcinomas were found in the larynx, trachea, bronchi, bronchioli, and alveoli of hamsters given varying doses of BP or DENA with or without AA. AA did not appear to act as a definite cofactor in respiratory tract carcinogenesis in this study. (14 refs)

- 79-6679 Synergistic Effect of Diethylstilbestrol on the Mutagenicity of 2-Acetylaminofluorene and N-Hydroxy-Acetylaminofluorene in the *Salmonella* Assay System. (Eng) Allaben, W. T. (Dept. Health, Education and Welfare, Food and Drug Admin., Natl. Center for Toxicological Res., Jefferson, AR 72079); Louie, S. C.; Lazear, E. J. *Cancer Lett* 7(2/3): 109-114; 1979.

Salmonella typhimurium, strain TA-1538, was used to study the mutagenic potentials of N-2-acetylaminofluorene (2-AAF, 2 and 4 μ g), N-hydroxy-N-2-acetylaminofluorene (N-OH-2-AAF, 1 and 3 μ g), and diethylstilbestrol (DES, 10 and 100 μ g) individually and in combination. In the presence of an induced or uninduced rat liver metabolizing system (S-9), the histidine-requiring strain of bacteria was reverted to prototrophy by 2-AAF and N-OH-2-AAF but not by DES. However, when DES was combined with 2-AAF or N-OH-2-AAF in the presence of the induced S-9 fraction, the number of revertant colonies was increased 2- to 4-fold above the levels obtained with the aromatic amines alone. The synergistic effect of the nonmutagenic DES on 2-AAF and N-OH-2-AAF mutagenicity was observed only when a 3-methylcholanthrene-induced rat liver S-9 fraction was used as the source of mammalian enzymes. When uninduced mouse or rat liver S-9 fractions were used in this test

system, an inhibitory rather than an enhancing effect was observed. (9 refs)

- 79-6680 Effect of pH on the Ratio of Substitution Products in DNA after Reaction with the Carcinogen N-Acetoxy-2-acetylaminofluorene. (Eng) Kriek, E. (Chemical Carcinogenesis Div., Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., Plesmanlaan 123, 1066 CX Amsterdam, Netherlands). *Cancer Lett* 7(2/3): 141-146; 1979.

The substitution reaction products of N-acetoxy-2-acetylaminofluorene (N-AcO-AAF) and the N-sulfate (potassium salt) of N-hydroxy-4-acetylaminobiphenyl (N-OSO₃K-AABP) with calf thymus DNA were determined after reaction in buffered soln of 0.10 M NaCl at pH values ranging from 4 to 9. With N-AcO-AAF, the ratio of N-(guanine-8-yl)-2-acetylaminofluorene to 3-(guanine-N²-yl)-2-acetylaminofluorene increased 2.2-fold over the entire pH range studied, starting at pH 9. With the N-OSO₃K-AABP, the total substitution of guanine was much lower (22-34 times) as compared with N-AcO-AAF; and the ratio of N-(guanine-8-yl)-4-acetylaminobiphenyl to 3-(guanine-N²-yl)-4-acetylaminobiphenyl was not affected by a change in pH of the reaction medium. As expected, heat-denatured DNA reacted more extensively with both esters, but an increase in substitution was much more pronounced for the biphenyl derivative (9 times) than for the fluorene compound (2.8 times). DNA degradation, denaturation, or interstrand cross-linking were not observed under the reaction conditions tested. (14 refs)

- 79-6681 Mutagenic Activation of N-Hydroxy-2-acetylaminofluorene by Developing Epithelial Cells of Rat Small Intestine and Effects of Antioxidants. (Eng) Schut, H. A. (Biochemical Pharmacology Section, Lab. Chemical Pharmacology, Div. Cancer Treatment, NCI, NIH, US Dept. Health, Education and Welfare, Bethesda, MD 20205); Thorgerirsson, S. S. *J Natl Cancer Inst* 63(6): 1405-1409; 1979.

The ability of subcellular fractions from male Sprague-Dawley rat small intestinal epithelial cells to activate N-hydroxy-2-acetylaminofluorene (AAF) to a mutagen for *Salmonella typhimurium* strain TA 1538 was studied. The mutagenicities of AAF samples activated by S9 fractions from villus tip and crypt cells and by cytosol were approx equal. Both the mutagenicity and N-hydroxy-2-acetylaminofluorene deacetylase activity with the S9 and cytosol fractions was inhibited by 10⁻⁵ M paraoxon; the inhibition was concentration dependent. The mutagenicity of the cytosol-activated AAF was increased by ascorbic acid, a max three- to fourfold increase being obtained with 10⁻³ M. Sodium selenite was toxic to the bacteria, especially in the absence of AAF. It was not mutagenic in the absence of AAF, but at 0.8 x 10⁻³ to 2 x 10⁻³ M, Na₂SeO₃ enhanced AAF mutagenicity. It is concluded that the mutagenic activation of AAF by subcellular fractions from villus tip and crypt cells was catalyzed by both a membrane-bound deacetylase(s) and soluble N-O-acyltransferase(s) and that these enzymes are expressed early in the differentiation of rat small intestinal epithelial cells. (41 refs)

- 79-6682 The Influence of 2-Acetylaminofluorene on the Dietary Induction of Pentose Phosphate Pathway Enzymes. (Ger) Fischer, W. (Pathologisches Institut,

Medizinischen Akademie Erfurt, Nordhauser Strasse 74, DDR-50 Erfurt, E. Germany); Grund, E. *Arch Geschwulstforsch* 49(5): 381-385; 1979.

The effect of feeding 2-acetyl-aminofluorene (AAF) on the induction of glucose-6-phosphate dehydrogenase (G-6-PDH) and 6-phosphogluconate dehydrogenase activities was studied in hooded rats (males, strain E, 180-220 g). AAF was mixed in the standard diet at 0.03%. Group 1 ate the AAF-diet for 2 wk, and group 2 for 4 wk. Group 3 received the AAF-diet for 4 wk, followed by standard diet for 2 wk. The animals were fasted for 3 days and then offered a diet containing 60% sucrose, 25% casein and 3% gelatin for 30 hr, after which they were killed. Liver G-6-PDH activity/g fresh wt after refeeding with the 60% sucrose diet increased 196-232%, 139%, 206%, and 188% above the fasting level in controls, group 1, group 2, and group 3, respectively. If the enzyme activities were expressed in units/g protein, enzyme induction in group 1 was only 75% of the induction achieved in controls; the amount of induction in groups 2 and 3 was similar to that of the corresponding controls. Little difference in induction of 6-phosphogluconate dehydrogenase was found for any of the AAF-fed groups. Metabolic effects of this type may be developed as quick tests for carcinogenicity. AAF inhibition of 6-phosphogluconate dehydrogenase activity induction has been observed previously. The lack of effect observed here may be due to the use of a different strain of rats. (6 refs)

- 79-6683 Induction of Foci of Altered Hepatocytes by a Single Injection of Azaserine to Rats. (Eng) Takahashi, S. (Dept. Pathology, Univ. Pittsburgh, Sch. Medicine, Pittsburgh, PA 15261); Katyal, S. L.; Lombardi, B.; Shinozuka, H. *Cancer Lett* 7(5): 265-272; 1979.

Experiments were carried out in male Wistar rats to determine whether foci of altered, γ -glutamyltranspeptidase (GGT)-positive hepatocytes could be elicited, under the promoting action of a choline-free diet, by a single ip injection of azaserine. After injection of azaserine (20 or 50 mg/kg), many foci developed in rats fed the choline-free diet containing acetylaminofluorene (AAF), but only a few occurred in rats fed a choline-supplemented (CS) diet containing AAF. Similar results were obtained in rats fed a plain choline-free diet or a plain CS diet and injected with a single dose of azaserine after partial hepatectomy. These findings indicate that azaserine is an effective initiator of liver carcinogenesis in rats, and that a CD diet acts as a strong promoter of the evolution of initiated liver cells to foci of altered, GGT-positive hepatocytes. (15 refs)

- 79-6684 Immunocytochemical Localization of Epoxide Hydrase in Hyperplastic Nodules Induced in Rat Liver by 2-Acetylaminofluorene. (Eng) Novikoff, A. B. (Dept. Pathology, Albert Einstein Coll. Medicine, Yeshiva Univ., 1300 Morris Park Ave., Bronx, NY 10461); Novikoff, P. M.; Stockert, R. J.; Becker, F. F.; Yam, A.; Poruchynsky, M. S.; Levin, W.; Thomas, P. E. *Proc Natl Acad Sci USA* 76(10): 5207-5211; 1979.

The localization of epoxide hydrase was examined in hyperplastic nodules induced in Sprague-Dawley rat liver by dietary 2-acetylaminofluorene. The nodules were separated from the livers; sections 15 μ m thick were prepared and exposed to medium containing Fab fragments of antibody specific to epoxide hydrase coupled to peroxidase. Thin sections were examined by electron microscopy. The nonparenchymal cells in the nodules were always

negative. Within the parenchymal cells, mitochondria and peroxisomes were always unreactive. Smooth endoplasmic reticulum (ER) and rough ER, including the nuclear envelope, were highly reactive. Thus, epoxide hydrase was visually demonstrated in the smooth and rough ER of hyperplastic liver nodules. However, the role, if any, of epoxide hydrase in the development of hepatocellular carcinoma remains unclear. (21 refs)

- 79-6685 Selenium Effects on the Carcinogenicity and Metabolism of 2-Acetylaminofluorene. (Eng) Marshall, M. V. (Biochemistry Dept., Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX 77030); Arnott, M. S.; Jacobs, M. M.; Griffin, A. C. *Cancer Lett* 7(6): 331-338; 1979.

Selenium (4 ppm in the drinking water) protected male albino rats fed diets containing 0.03% 2-acetylaminofluorene (AAF) against hepatic damage and also produced at least a 50% reduction in liver tumor incidence. In an in vitro assay system utilizing microsomes from Se-supplemented or nonsupplemented 3-methylcholanthrene (MC, 80 mg/kg)-induced rats, Se administration po affected AAF metabolism by leading to an increase in ring hydroxylation and a decrease in N-hydroxylation. Addition of Se to the microsomal assay system increased 3-OH-AAF formation and decreased N-OH-AAF formation, thus shifting the metabolic balance toward detoxification pathways. (11 refs)

- 79-6686 In Vivo Induction of Sister-Chromatid Exchanges in Liver and Marrow Cells by Drugs Requiring Metabolic Activation. (Eng) Schreck, R. R. (Div. Clinical Genetics, Mental Retardation Center, Children's Hosp. Medical Center, Boston, MA 02115); Paika, I. J.; Latt, S. A. *Mutat Res* 64(5): 315-328; 1979.

A highly sensitive method is presented for the detection of in vivo induction of sister-chromatid exchange (SCE) in mice subjected to partial hepatectomy. SCE induction by either acetylaminofluorene (AAF) or cyclophosphamide, both of which require metabolic activation, was significantly greater in both regenerating liver and bone-marrow cells of partially hepatectomized animals than in marrow cells of intact mice. These experiments confirm the ability of AAF, a well known mutagen-carcinogen, to induce SCE formation, even though the cytogenetic effects of this drug on nonhepatectomized mice is very small. The in vivo system described demonstrates the influence of the liver on drug-induced damage to extra-hepatic tissues. The procedures developed should facilitate the detection of drug-induced cytogenetic damage and permit the comparison of intertissue differences in SCE induction with tissue-specific differences in drug-activation pathways. (48 refs)

- 79-6687 Enhancing Effect of Inducers of Liver Microsomal Enzymes on Induction of Hyperplastic Liver Nodules by N-2-Fluorenylacetamide in Rats. (Eng) Tatematsu, M. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Japan); Nakanishi, K.; Murasaki, G.; Miyata, Y.; Hirose, M.; Ito, N. *J Natl Cancer Inst* 63(6): 1411-1416; 1979.

The effects of inducers of liver microsomal enzymes on the induction of hyperplastic liver nodules by N-2-fluorenylacetamide

(FAA: 200 ppm in the diet for 2 wk) were studied in male F344 rats. The test compounds were given in the diet for 8 wk following FAA treatment, and partial hepatectomies were performed during the first wk after FAA treatment. Small foci were grossly visible on the livers of hepatectomized animals given FAA and polychlorinated biphenyls (PCB: 500 or 1,000 ppm), 3-methylcholanthrene (MCA: 70 ppm), phenobarbital (PB: 500 ppm), and/or β -naphthoflavone (NF: 500 ppm). The numbers of hyperplastic nodules in these animals and those given FAA plus 3-(3,5-dichlorophenyl)-5,5-dimethyl-oxazoline-dione-2,4 (DDOD) were significantly greater than those given FAA only. Animals given 1,000 ppm PCB plus FAA had more small nodules than those given FAA only and more than those given any of the other compounds plus FAA. Partial hepatectomy during PCB, PB, MCA, DDOD, and NF administration enhanced the induction of hyperplastic liver nodules by FAA. (37 refs)

79-6688 Persistence and Growth of Rat Liver Neoplastic Nodules Following Cessation of Carcinogen Exposure. (Eng) Hirota, N. (Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Rd., Valhalla, NY 10595); Williams, G. M. *J Natl Cancer Inst* 63(5): 1257-1265; 1979.

The fate of neoplastic liver nodules following the cessation of exposure to N-2-fluorenylacetamide was studied in male F344 rats. Altered (hyperplastic) foci and neoplastic (hyperplastic) nodules identified by their resistance to iron accumulation were induced in the livers of rats by limited feeding of the carcinogen for three, four, or five cycles of 4-wk intervals separated by 1 wk of a basal diet. Foci were present by the end of three feeding cycles and increased in number with further carcinogen exposure. No nodules were present at the end of three or four cycles, but they appeared at later intervals after removal of the carcinogen. Nodules were present at the end of five cycles of feeding and increased in number later. Thus, nodules were found to be persistent and to have the progressive growth ability in situ that is characteristic of neoplasms. (49 refs)

79-6689 Opposite Effects of Lead on Chemical Carcinogenesis in Kidney and Liver of Rats. (Eng) Hinton, D. E. (Comparative and Environmental Pathobiology Program, Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD 21201); Lipsky, M. M.; Heatfield, B. M.; Trump, B. F. *Bull Environ Contam Toxicol* 23(4/5): 464-469; 1979.

The effects of lead (incorporated in the diet as 1% lead acetate) and N-(4'-fluoro-4-biphenyl)acetamide (FBPA: 0.04% of the diet) on the development of renal adenocarcinomas (RA) and hepatocellular carcinomas (HCC) in male Fischer-344 rats were studied. The incidence of RA was higher in animals given both lead and FBPA (group 4) than in those given lead (group 3) or FBPA (group 2) alone or those given a control diet. The tumors produced by FBPA alone were histologically identical to those produced by lead plus FBPA. The RA were larger and the precancerous kidney lesions more numerous and faster growing in group 4 than in the other groups. Only a few formative lesions were observed in group 3 rats. Liver wt was increased in group 2 and, to a lesser extent, in group 4, but not in group 3, relative to that in controls. HCC developed several weeks earlier in group 2 than in group 4, which might suggest a possible retarding effect of lead. Lead also appeared to inhibit cytochrome P-450, whereas

FBPA induced it. The data indirectly suggest that the mixed-function oxidase system mediates FBPA carcinogenicity. (17 refs)

79-6690 Further Studies on the Carcinogenicity of a Food Additive, AF-2, in Hamsters. (Eng) Kinebuchi, M. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan); Kawachi, T.; Matsukura, N.; Sugimura, T. *Food Cosmet Toxicol* 17(4): 339-341; 1979.

The carcinogenicity of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), once used as a food additive, was administered to golden hamsters of both sexes for 660 days at a level of 0.08 or 0.16% in the basal diet. The first forestomach tumors were detected on days 498 and 659 in the males and on days 444 and 451 in the females of the groups fed 0.08 and 0.16% AF-2, respectively. Respective incidences at day 660 in the two dosage groups were 65% and 100% in the males and 58% and 76% in the females. These tumors were squamous cell carcinomas of the forestomach in 15% and 47% of males and 0% and 6% of females given 0.08% and 0.16% AF-2, respectively. Esophageal tumors were found only in hamsters given 0.16% AF-2, the incidence being 35% in males and 6% in females. No tumors were found in other organs with the exception of one adrenal pheochromocytoma in a female given 0.08% AF-2. In the control groups, no tumors were observed in any organs examined. (15 refs)

79-6691 Differential Excision from DNA of the C-8 Deoxyguanosine Reaction Products of N-Hydroxy-2-aminofluorene and N-Acetoxy-N-acetyl-2-aminofluorene by Endonuclease S1 from *Aspergillus oryzae*. (Eng) Kriek, E. (Chemical Carcinogenesis Div., Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., Plesmanlaan 123, 1066 CX Amsterdam, Netherlands); Spelt, C. E. *Cancer Lett* 7(2/3): 147-154; 1979.

Calf thymus DNA was modified in vitro with either [G-³H]N-hydroxy-2-aminofluorene (AF) or [G-³H]N-acetoxy-N-acetyl-2-aminofluorene (AAF), and the nuclease S₁ digestion was studied under identical conditions. The ratios of the max reaction rate (V) and the Michaelis constant (K_m), V/K_m, indicate that AF-modified DNA was hydrolyzed three times more slowly than AAF-modified DNA under similar reaction conditions. The AF-modified DNA was slightly more susceptible to partial digestion by nuclease S₁ than unmodified control DNA. These results suggest that the local regions of denaturation induced by AF substitution are smaller than those associated with AAF modification. (13 refs)

79-6692 Mutagenic Activity of Gastric Juice. (Eng) Montes, G. (Sch. Medicine, Universidad del Valle, Cali, Colombia); Cuello, C.; Gordillo, G.; Pelon, W.; Johnson, W.; Correa, P. *Cancer Lett* 7(6): 307-312; 1979.

Gastric juice samples were taken from a rural Colombian Andes population at high risk for gastric cancer and tested for mutagenesis with *Salmonella typhimurium* strains TA100 and TA1538. Direct mutagenic effect was found in samples with detectable amounts of nitrite. However, up to 25 ppm nitrite alone did not result in detectable mutagenicity in this test system; thus the mutagenicity of the gastric juice samples (containing <9 ppm nitrite) could not be attributed to nitrite alone. Nitrite-negative

samples from the same area and samples from the low-risk area of Cali were negative using the same mutagenesis assay. (13 refs)

- 79-6693 Identification of Nitrohexane in Corn Treated with Nitrous Acid. (Eng) Hansen, T. J. (Dept. Medical Biophysics, Univ. Toronto, Toronto, Canada M4X 1K9); Archer, M. C.; Tannenbaum, S. R. *J Agric Food Chem* 27(5): 1072-1075; 1979.

Corn samples from Massachusetts and from a region of Colombia with a high incidence of stomach cancer were reacted with nitrite under acidic conditions. The major product formed was nitrohexane. Nitroalkanes represent a new class of compounds that may be present in certain foods or form in the stomach in the presence of nitrite. They give a positive thermal energy analysis response and may consequently interfere in the analysis of N-nitrosamine formation. Use of an auxiliary method such as UV photolysis would allow distinction between the two classes of compounds. (24 refs)

- 79-6694 Interaction of Wheat Bran with Nitrosamines and with Amines During Nitrosation. (Eng) Wishnok, J. S. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Richardson, D. P. *J Agric Food Chem* 27(5): 1132-1134; 1979.

The extent of binding of a representative sample of nitrosamines to a standard bran was measured, and the effect of bran on the rate of formation of nitrosamines from amines and nitrite was determined. Nitrosamines were adsorbed by wheat bran, the extent of binding apparently being related to the structure of the nitrosamine. The rate of formation of N-nitrosodipropylamine was increased when the nitrosation of dipropylamine was carried out in the presence of bran. If the intestine is protected from exposure to nitrosamines by the binding of these compounds to fiber, then this protection may be less effective with the more potent carcinogens. (19 refs)

- 79-6695 Mutagenicity of Nitrosodiethanolamine on *Salmonella Typhimurium*. (Eng) Hesbert, A. (INRS, Avenue de Bourgogne, 54500 Vandoeuvre-les-Nancy, France); Lemonnier, M.; Cavelier, C. *Mutat Res* 68(3): 207-210; 1979.

The mutagenicity of nitrosodiethanolamine (NDEA) was examined in the Ames test using *Salmonella typhimurium* (TA100, TA98, TA1538, and TA1535) in the presence or absence of S9 mouse liver mix. NDEA exhibited mutagenic effects in TA100 and TA1535 in the absence of S9 mix at doses ranging from 1 to 10 μ l/plate; with or without the activation system, a linear relationship between dose and response was obtained. At higher doses, NDEA appeared to be mutagenic per se to TA100 and TA1535 and did not seem to require activation by enzymes to produce reactive electrophilic intermediates. These data indicate that further studies of the mutagenicity and carcinogenicity of NDEA (detected as a contaminant in synthetic cutting fluids) are needed. (13 refs)

- 79-6696 Detection of N-Nitrosodiethanolamine in Human Urine Following Application of a Contaminated Cosmetic. (Eng) Edwards, G. S. (New England Inst. Life Sciences, Waltham, MA 02154); Peng, M.; Fine, D. H. *Toxicol Lett* 4(3): 217-222; 1979.

High pressure liquid chromatography with nitrosamine detection was used to determine the presence of urinary N-nitrosodiethanolamine (NDEIA) following the application of an NDEIA-contaminated (77 ppm) cosmetic to the chest and back of a male subject. NDEIA was found in urine samples collected between 1 and 13 hr after application of the cosmetic. At least 17.3 μ liters of NDEIA were excreted in the urine during this period. Thus, NDEIA is absorbed from human skin to which a widely used facial cosmetic has been applied. (10 refs)

- 79-6697 The Influence of 5-Nitro-2-Furyl Acrylic Acid on Human Fibroblasts Cultivated In Vitro. (Eng) Slamenova, D. (Cancer Res. Inst. Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Mazariova, O. *Neoplasma* 26(3): 267-274; 1979.

The effects of 5-nitro-2-furyl acrylic acid (NFA: 2-100 5mg/ml) on the synthesis of macromolecules by EUE human fibroblasts were studied in vitro. NFA in all concentrations had a cytostatic and/or cytotoxic effect on the cells, the reduction in cells being dependent on the NFA concentration. One of the first manifestations of the effect of NFA was stimulation of the incorporation of 14 C-thymidine (Tdr). Decreased Tdr incorporation was observed after prolonged NFA treatment or in the presence of high concentrations of NFA. In cells treated for 2 hr with NFA and then removed to control medium, a persistent cytostatic and/or cytotoxic effect was observed. DNA synthesis in such cells was inhibited in a dose-dependent fashion, and RNA synthesis and protein synthesis were inhibited by higher doses of NFA. The treated cells never showed recovery of DNA synthesis to control levels, even after treatment with the lowest concentration of NFA. (8 refs)

- 79-6698 Effects of Urethan, Dimethylnitrosamine, Paraquat, and Butylated Hydroxytoluene on the Activity of Lactic Acid Dehydrogenase and Isoenzyme Spectrum in the Mouse Lung. (Hun) Rady, P. (Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudományi Egyetem, Debrecen, Hungary); Arady, I.; Bojan, F. *Egeszsegtudomány* 23(3): 251-255; 1979.

The effects of urethan (1,000 mg/kg, ip), dimethylnitrosamine (DMNA: 10 mg/kg, ip), paraquat (20 mg/kg, ip), and butylated hydroxytoluene (BHT: 800 mg/kg, ip) on lung lactate dehydrogenase (LDH) activity was studied in LATI:CFLP male and female mice. Total lung LDH activity was increased significantly by the carcinogenic substances DMNA and urethan 7 days after treatment. LDH activity showed a further increase, almost reaching levels as high as those found in tumors induced within 35 days by these substances in preliminary experiments. Paraquat and BHT caused only a transient increase in LDH activity. The ratio of the H and M isoenzymes decreased steadily in the lungs of mice treated with urethan (0.782 on day 0, 0.627 on day 7, and 0.399 on day 35) and DMNA (0.787 on day 0, 0.658 on day 7, and 0.491 on day 35). The increase in LDH activity can be partly explained by the fact that chemically induced pulmonary adenomas of the mouse lung originate from type II pneumonocytes, which have an inherently higher LDH activity than do the other cells forming the alveolar tissue. Thus, the increased total LDH activity is due to the proliferation of type II pneumonocytes. (19 refs)

- 79-6699 Enhancement of Adenoma Formation in Mouse Lung by Butylated Hydroxytoluene. (Eng) Witschi, H.

(Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN 37830); Lock, S. *Toxicol Appl Pharmacol* 50(3): 391-400; 1979.

Temporal relationships between urethan and butylated hydroxytoluene (BHT) in the enhancement of lung tumor formation were studied. Male Swiss-Webster mice (aged 6-8 wk) received a single dose of urethan (50, 100, 250, or 1,000 mg/kg, ip), which produces lung adenomata 14-24 wk after administration. Urethan-treated mice were injected with BHT (300 mg/kg, ip, 1x/wk x 13) starting 1 wk after urethan injection. The number of tumors per lung at 14 wk after urethan treatment was significantly increased by BHT at doses of 100-1,000 mg/kg and at 24 wk by doses of 250 and 1,000 mg/kg. Increased numbers of tumors per lung were also found when the interval between urethan injection and the first BHT treatment was extended up to 6 wk and when only four BHT injections were given. Pretreatment with 13 weekly BHT injections, followed 1 wk later by 1,000 mg/kg of urethan had no effect on the number of lung tumors. In 6- to 8-wk-old Balb/c mice, the simultaneous administration of urethan (500 mg/kg, ip) and BHT (400 mg/kg, ip) resulted in a decrease in the number of tumors per lung. In three mouse strains that are resistant to adenoma formation, treatment with BHT following urethan injection did not significantly increase tumor incidence or the av number of tumors per lung. These results suggest that BHT has several properties of a promoting agent for urethan-initiated adenoma formation. (30 refs)

79-6700 Concentration-dependent Mutation by Alkylating Agents in Human Lymphoblasts and *Salmonella typhimurium*: N-methyl-N-nitrosourethane and β -Propiolactone. (Eng) Penman, B. W. (Dept. Nutrition, Massachusetts Inst. Technology, Cambridge, MA 02139); Hoppe, H.; Thilly, W. G. *J Natl Cancer Inst* 63(4): 903-907; 1979.

The toxic and mutagenic effects of the alkylating agents N-methyl-N-nitrosourethane (MNUT) and β -propiolactone (BPL) were measured quantitatively in human lymphoblasts and *Salmonella typhimurium*. Forward mutation to 6-thioguanine resistance was measured in the human lymphoblasts, and forward mutation to 8-azaguanine resistance was measured in the bacterial cells after equigenerational (1.5 doubling times) exposures. In both systems, the induced mutant fraction rose linearly as a function of concentration for BPL and was biphasic for MNUT. The responses of the two assay systems to eight alkylating agents were compared. The exposure of the cells to each alkylating agent was calculated as exposure concentration multiplied by the time of exposure, and allowance was made for the decomposition of the alkylating agent during exposure (integral exposure). Human cells were 2.5-13 times more sensitive than was *S. typhimurium* to the alkylating agents methyl methanesulfonate, ethyl methane-sulfonate, propyl methane-sulfonate, N-methyl-N-nitro-N-nitrosoguanidine, methyl nitrosourea, and MNUT. *S. typhimurium* cells were 3 times more sensitive to butyl methane-sulfonate and 25 times more sensitive to BPL than were human cells. (17 refs)

79-6701 Carcinogenic Effect of N-Ethyl- and N-Amyl-N-Nitrosourethans on Female Donryu Rats. (Eng) Hirose, M. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Maekawa, A.; Kamiya, S.; Odashima, S. *Gann* 70(5): 653-662; 1979.

The carcinogenicity of N-ethyl-N-nitrosourethan (ENUR) and N-amyl-N-nitrosourethan (ANUR) was tested in female Donryu rats. One group of 45 rats received 400 ppm ENUR in the drinking water for 6 days, followed by 200 ppm for 4 days. After a 7-day period without treatment, the animals received a 100 ppm ENUR soln (15-20 ml/rat/day) for life. Another group of 54 rats received a 400 ppm ANUR soln (15-20 ml/rat/day). A third group of 14 rats was treated topically with 0.03 ml ENUR 2x/wk. All rats had died by the 385th day of the experiment. Of the 35 rats given ENUR po, all developed tumors in the forestomach, 28 in the esophagus, 25 in the duodenum, 16 in the oral cavity and pharynx, and 18 in the liver. Topical application of ENUR also resulted in tumors in the forestomach (13/13), skin (11/13), and liver (1/13). Of the rats given ANUR, 39/40 developed tumors in the esophagus, 37/40 in the oral cavity and pharynx, and 31/40 in the forestomach. Comparison of these results with those induced by N-methyl-N-nitrosourethan, N-propyl-N-nitrosourethan, and N-butyl-N-nitrosourethan (BNUR) indicated that the incidence of tumors in the esophagus and oral cavity and pharynx increase in proportion to the mol wt of the alkyl chain, while the incidence of cancer of the forestomach decreases. The results also indicate that ENUR induces tumors both directly (skin tumors) and indirectly (tumors of the forestomach and liver). (21 refs)

79-6702 Bioassay of Sulfallate for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Tech Rep Ser* (115): 59 pp.; 1978.

Sulfallate was investigated for possible carcinogenicity by adding it to the feed of Osborne-Mendel rats and B6C3F1 mice. Groups of 50 males and 50 females of each species received sulfallate at either of two concentrations: The time-weighted av high and low dietary concentrations were, respectively, 410 and 250 ppm for male rats, 404 and 250 ppm for female rats, 1,897 and 949 ppm for male mice, and 1,815 and 908 ppm for female mice. The dosing period of 78 wk was followed by an observation period of 25-26 wk for dosed rats, 33 wk for control rats, and 12-13 wk for dosed and control mice. From wk 30 to wk 78, an unusually high incidence of signs characteristic of eye irritation was observed in the dosed animals. Statistical analysis demonstrated that sulfallate administration was associated with increased incidences of mammary adenocarcinomas in female rats and of stomach and thyroid neoplasms in male rats. There were significant positive associations between dose incidence of mammary adenocarcinomas in female rats and between dose and incidence of tumors in male rats. In mice, long-term sulfallate administration was associated with increased incidences of neoplastic lesions including mammary adenocarcinomas in females; squamous cell carcinomas of the skin, adnexal tissues, and stomach in males and females; lung tumors in males and females; and hepatocellular carcinomas in females. Sulfallate administration was also associated with a significantly increased incidence of alveolar/bronchiolar neoplasms in male mice and of mammary adenocarcinomas without and with squamous metaplasia in female mice. Rare esophageal tumors (ie, one papilloma and two squamous cell carcinomas) occurred in high-dose rats but not in control and uncommon skin, and forestomach carcinomas were observed in sulfallate-treated mice. (17 refs)

79-6703 Role of Hormone Imbalance in Transplacental Carcinogenesis Induced in Syrian Golden Hamsters by Sex Hormones. (Eng) Rustia, M. (Eppley Inst. Res. Cancer, Univ.

Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NE 68105). *Natl Cancer Inst Monogr* (51): 77-87; 1979.

Single, simultaneous doses of ethylurea (EU: 100 mg/kg) and NaNO_2 (50 mg/kg), precursors of the carcinogen ethylnitrosourea (ENU), were administered to pregnant Syrian golden hamsters by intragastric intubation on days 12, 13, 14, or 15 of gestation. A progressively increasing high incidence of peripheral nervous system (PNS) tumors occurred in progeny of these hamsters. The incidence was higher in female progeny than in males. In further experiments, multiple doses of 100 mg/kg EU and 50 mg/kg NaNO_2 were administered to pregnant females from days 12-15. Total amounts equaled 400 mg/kg EU and 200 mg/kg NaNO_2 . Female progeny again developed a greater number of PNS tumors than the males. At 60 wk of age, the PNS tumor incidence was 64% in females, with 3.8 tumors/animal, and 12.5% in males at a rate of 1 tumor/animal. By 60 wk all females were dead, but 69% of the males had survived. Observation extended through the male life span (108 wk) revealed that at death 56.3% of the males had developed tumors. Thus, the overall tumor incidence was similar in both sexes, but female progeny developed a significantly greater number of tumors/animal (3.8 vs 1.4) within a significantly shorter latency period (41 vs 72 wk). In another series of studies, progeny were gonadectomized at 5 wk of age. Orchidectomized males developed a significantly higher tumor incidence (85% vs 56%) and a significantly greater tumor multiplicity (3.8 vs 1.4) within a shorter latency period (72 vs 51 wk). The percentage of all tumor types was also greater in gonadectomized males than in females. Females showed an increase in different tumor types, but they had fewer tumors/animal. These results suggest that endogenously generated androgens may inhibit PNS tumor development. Adult hamsters treated with EU and NaNO_2 at doses 10 times greater than those given in the transplacental experiments had PNS tumor incidence three- to fourfold lower than that of prenatally exposed progeny; only 18%-20% of the adults developed PNS tumors. The tumor spectrum was wider, however, and the overall tumor incidence was as high as that in transplacentally exposed or gonadectomized progeny. It was concluded that neural tissues become less sensitive to neoplastic change during the postnatal period, but that susceptibility of other tissues increased. To simulate human prenatal exposure to diethylstilbestrol (DES), pregnant hamsters were given a single dose of 20-40 mg/kg DES on day 15 of gestation or two consecutive doses of 20 or 40 mg/kg on days 14 and 15. Over 28% of female progeny exposed to a single dose and 50% exposed to two doses developed reproductive tract neoplasms. Metaplastic, hyperplastic, and dysplastic lesions increased with increased DES exposure. Male progeny developed tumors of the epididymis (70%) and of the testis (40%). (32 refs)

79-6704 Methylation of Neuronal and Glial Macromolecules by Methylnitrosourea and Dimethylnitrosamine In Vivo. (Eng) Hemminki, K. (Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland); Savolainen, H. *Toxicol Lett* 4(4): 287-293; 1979.

Rats were injected ip with a mixture of 50 μCi of radioactive methylnitrosourea (1.0 Ci/mmol) and dimethylnitrosamine (25.7 mCi/mmol), and neuronal and glial cell fractions were separated from brain tissue after 4 hr, 72 hr and 10 days. DNA, RNA and protein were purified; and specific radioactivity was determined. All labeling times with methylnitrosourea neuronal nucleic acid were methylated to higher (1.5-2.0:1) specific radioactivity than glial nucleic acids. 7-Methylguanine appeared to be the major purine adduct and O⁶-methylguanine a minor adduct in the two cell fractions. The proportion of O⁶-methylguanine was equal in

the two cell fractions. With dimethylnitrosamine, glial macromolecules were methylated to a greater extent than neuronal macromolecules. Neuronal cells appear to be inactive in the metabolism of dimethylnitrosamine. The level of methylation in brain tissue by dimethylnitrosamine was of a lower order than in liver tissue. (18 refs)

79-6705 Unscheduled DNA Synthesis in Isolated Hepatic Nuclei After Treatment of Rats with Methylnitrosourea In Vivo. (Eng) Kaufmann, W. K. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143); Kaufman, D. G.; Grisham, J. W. *Biochem Biophys Res Commun* 91(1): 297-302; 1979.

Unscheduled DNA synthesis was measured in vitro in nuclei isolated from nonreplicating liver cells from male F344 rats treated iv with methylnitrosourea (MNU). MNU significantly stimulated the capacity of such nuclei to incorporate deoxyribonucleoside-5'-triphosphate precursors into nuclear DNA in vitro ($p < 0.01$). Max rates of DNA synthesis were observed in nuclei isolated from livers 10 and 45 min after injection of 0.25 mmole/kg MNU. In nuclei isolated 12 hr after treatment, the rate of endogenous DNA synthesis had returned to near control levels. The response was dependent on the dose of MNU between 0.05 and 0.10 mmole/kg, but there appeared to be a plateau in the effect at doses > 0.10 mmole/kg. The MNU-activated nuclear DNA synthesis was a template-directed, gap-filling process. It appears to represent the continuation in vitro of unscheduled, reparative DNA synthesis initiated in damaged cells in vivo. (18 refs)

79-6706 Effect of N-Carboxymethyl-N-Nitrosourea on Viability and Mutagenic Response of Repair-deficient Strains of *Escherichia coli*. (Eng) Yoshikawa, K. (Dept. Mutagenesis, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan); Uchino, H.; Yamamoto, M.; Yamada, T.; Tanimura, A.; Kondo, S. *Gann* 70(5): 705-708; 1979.

Under simulated human gastric conditions, the glycoamine found in meats is converted into N-carboxymethyl-N-nitrosourea (CMNU) by reaction with sodium nitrite. CMNU was tested for mutagenicity and lethal activity with a set of isogenic strains of *Escherichia coli* possessing the same auxotrophic marker but different DNA-repair capacities. Both strains NG30 (*recA*⁻) and R15 (*polA*⁻) were far more sensitive to lethality induced by CMNU than were H/r30R (wild) and Hs30R (*uvrA*⁻) strains. The *uvrA*⁻ strain was more sensitive to mutation induction by CMNU than the wild and *polA*⁻ strains, but the *recA*⁻ strain was barely susceptible to CMNU mutation. It was concluded that the major cause of CMNU lethality in *E. coli* is different from that of mutation induction. (17 refs)

79-6707 Comparative Binding Studies on 1,1'-Ethylene-bis(1-nitrosourea) and Some 1-Alkyl-1-nitrosoureas with Nucleic Acids and Proteins In Vitro. (Eng) Morimoto, K. (Div. Medical Chemistry, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan); Tanaka, A.; Yamaha, T. *Gann* 70(5): 693-698; 1979.

The binding capacities of 1,1'-ethylene-bis(1-nitrosourea) (EBNU), 1-methyl-1-nitrosourea (MNU), 1-ethyl-1-nitrosourea

(ENU), and 1-propyl-1-nitrosourea (PNU), labeled with ^{14}C in the carbonyl or alkyl group, to nucleic acids, proteins, and synthetic biopolymers was compared in vitro. The binding of radioactivity from the labeled ^{14}C -carbonyl group of EBNU to proteins and polypeptides was at least twofold higher than that of MNU, ENU, and PNU. The alkylating activity to DNA decreased in the order of MNU, EBNU, and ENU. PNU did not bind with DNA to any detectable extent. Binding of radioactivity from EBNU-[ethylene- ^{14}C] was found in histone, but binding from each mono-N-nitrosourea-[alkyl- ^{14}C] did not occur. The effect of various amino acids on the binding of ^{14}C -EBNU and ^{14}C -MNU to polylysine and poly(G) was studied. All the amino acids tested had no or little effect except cysteine. The binding of radioactivity from the carbonyl- ^{14}C group of EBNU and MNU to polylysine decreased about 30% and 20%, respectively, in the presence of equimolar amounts of cysteine. Cysteine completely inhibited the binding of radioactivity from EBNU[ethylene- ^{14}C] to polylysine and poly(G), but binding of radioactivity from MNU[methyl- ^{14}C] to poly(G) was inhibited only slightly. (20 refs)

- 79-6708 1-Methyl-1-Nitrosourea Induction of Cancer in a Localized Area of the Syrian Golden Hamster Trachea. (Eng) Grubbs, C. J. (Div. Life Sciences, I.I.T. Res. Inst., 10 West 35th Street, Chicago, IL 60616); Moon, R. C.; Norikane, K.; Thompson, H. J.; Becci, P. J. *Prog Exp Tumor Res* 24: 345-355; 1979.

A respiratory tumor model was developed that permits the rapid induction of cancer in a localized area of the hamster trachea. The predominant type of cancer induced was combined epidermoid and adenocarcinoma similar to bronchogenic carcinoma in humans. The intratracheal instillation of either 0.5% or 2.5% 1-methyl-1-nitrosourea 1x/wk for 15 consecutive wk induced a 68% and 33% incidence of tracheal cancers, respectively, within 6 mo. This treatment regimen permits tumor development in a large number of animals without toxic effects and thus provides a model for use in the rapid evaluation of newly synthesized anticancer compounds. (20 refs)

- 79-6709 Mechanism of Perinatal Tumor Induction by Neuro-Oncogenic Alkylnitrosoureas and Dialkylaryltriazenes. (Eng) Kleihues, P. (Abteilung Neuropathologie, Pathologisches Institut der Universität Freiburg, 78 Freiburg, W. Germany); Cooper, H. K.; Buecheler, J.; Kolar, G. F.; Diessner, H. *Natl Cancer Inst Monogr* (51): 227-231; 1979.

The methylation by 3,3-dimethyl-1-phenyltriazenes and N-methyl-N-nitrosourea (MNU) of DNA from BD-IX rat liver and brain was investigated at various developmental stages. Following a single sc injection of [^{14}C]DMPT (100 mg/kg, 15 hr survival time) in pregnant rats (21st day of gestation), the extent of methylation of purine bases was similar in fetal liver and brain. During postnatal growth, this treatment resulted in an increasingly preferential methylation of liver DNA. In 30-day-old BD-IX rats, 7-methylguanine concentrations were approx eight times higher in liver than in brain DNA. This suggested that during prenatal development, both liver and brain DNA are transplacentally methylated by a proximate carcinogen produced by maternal organs. After a single ip injection of [^3H]MNU (10 mg/kg) to 10-day-old rats, O⁶-methylguanine was removed more rapidly from hepatic than from cerebral DNA. Within 1 wk of the injection, the brain-to-liver ratio for O⁶-methylguanine increased from 1.4 to 98.

These results are compatible with the hypothesis that the deficiency of various organs for repair excision of O⁶-alkylguanine from DNA correlates with their susceptibility to malignant transformation by monofunctional alkylating carcinogens. (25 refs)

- 79-6710 Studies with a New Experimental Model in Respiratory Carcinogenesis. (Eng) Nettesheim, P. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Yarita, T. *Prog Exp Tumor Res* 24: 330-344; 1979.

A new experimental model for respiratory carcinogenesis was studied using hamsters and N-nitroso-N-methylurea (NMU). After 5-10 exposures to 1% NMU with the new tracheal exposure device, the tracheal epithelium changed to a low cuboidal epithelium with areas of flat and 'bizarre' cells. Other areas showed hyperplastic and hypertrophic epithelium with small squamous metaplasias. These changes were more widespread and severe after 15-20 exposures, and small early invasive carcinomas were observed in many animals after 20 exposures. In general, the toxic changes were more severe in animals receiving two exposures/wk than in those exposed only once/wk. With 0.5% NMU, the mucosal changes were milder; and with 0.25% NMU, changes other than mild hyperplasia were rare. With increasing numbers of exposures to 1% NMU, the number of tumor-bearing and invasive-tumor-bearing animals increased and the tumor induction time decreased. The tumor incidence was only 10%-20% lower after exposure to 0.5% NMU than after similar exposure to 1% NMU, but the same mean tumor induction times were 10-14 wk longer with the lower concentration. Benign polyps and papillomas comprised 40% or more of the tumors in the low-dose groups, whereas invasive carcinomas comprised 50%-70% of all tumors in the high-dose groups. Of the invasive carcinomas, 50% were epidermoid carcinomas and 20% each were adenocarcinomas and large cell carcinomas. Small cell and squamous type carcinomas in situ were observed, as were anaplastic large cell and small cell carcinomas. Distant metastases were not observed. Most of the neoplasms occurred in the region between the sixth and thirteenth tracheal rings. (8 refs)

- 79-6711 Bioassay of Trimethylthiourea for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (129): 44 pp.; 1979.

The possible carcinogenicity of trimethylthiourea was tested by feeding groups of 50 F344 rats or B6C3F1 mice of each sex a diet containing either of two concentrations of the test chemical (500 and 250 ppm for rats; 1,000 and 500 ppm for mice) for 77 wk. Groups of 20 matched animals fed a normal diet were used as controls. The treatment period was followed by an observation period lasting 29 wk for rats and 14 wk for mice. No correlation between treatment and mortality was observed. The mean body wt of high-dose female rats and treated mice of both sexes was significantly lower than those of control animals. A significantly increased incidence of follicular-cell carcinomas of the thyroid and of combined follicular-cell carcinoma and follicular-cell adenoma was observed in female rats; these incidences were dose-related. It is concluded that under the conditions of the assay, trimethylthiourea is carcinogenic in female F344 rats. (24 refs)

- 79-6712 Synthesis of 1-(2-Hydroxyethyl)-nitrosourea and Comparison of Its Carcinogenicity with That of 1-Ethyl-1-nitrosourea. (Eng) Swenson, D. H. (Natl. Center Tox-

icological Res., Jefferson, AR 72079); Frei, J. V.; Lawley, P. D. *J Natl Cancer Inst* 63(6): 1469-1473; 1979.

1-(2-Hydroxyethyl)-1-nitrosourea (HNU) was prepared by the action of nitrosyl chloride on (2-hydroxyethyl)urea, and its carcinogenicity for female C57BL/Cbi mice was compared with that of 1-ethyl-1-nitrosourea (ENU). The ether-water partition coefficient of the HNU obtained was 0.06, compared with a previously reported value of 0.39. Similarly, the half-life of HNU following hydrolysis at pH 7 and 37 C for 1 hr was 0.17 hr, compared with a much higher value previously reported. There was also a lack of complete agreement between the physical and chemical data obtained for the HNU and that previously reported. The potency of HNU in inducing thymic lymphocytic lymphomas was close to that of ENU. The slope of the dose-response curve for HNU (log scales) was 2.4, indicating that tumor induction was a 2- to 3-hit process. (27 refs)

79-6713 Bioassay of Nithiazide for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* 152(146): 46 pp.; 1979.

A bioassay of nithiazide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice of either sex at either of two concentrations (1,250 and 625 ppm for rats, 5,000 and 2,500 ppm for mice) for 113 wk. Because of a shortage of nithiazide, the animals were fed a normal diet for a period of 9 wk in the course of the assay. No correlation between treatment and mortality was observed, but treatment-related mean body wt depression was noted. A significantly high incidence of hepatocellular carcinoma was observed in the high-dose male mice; a nonsignificantly higher incidence was observed in female mice. A significantly increased incidence of a combination of mammary and skin fibroadenomas and cystadenomas NOS in the high-dose female mice and of mammary neoplasms in female rats was observed. It is concluded that, under the conditions of the assay, nithiazide is carcinogenic for B6C3F1 mice of both sexes and for female F344 rats. (14 refs)

79-6714 Induction of Tumors by Direct Injection of *N*-Ethyl-*N*-nitrosourea Into the Amniotic Space of the Mouse Fetus. (Eng) Rossi, L. (Inst. Oncology, Univ. Genova, Viale Benedetto XV, 10 Pad. B-1632, Genoa, Italy); Mollner, T.; Munhall, A.; Shubik, P. *J Natl Cancer Inst* 63(4): 987-989; 1979.

An *N*-ethyl-*N*-nitrosourea (ENU) solution was injected into the amniotic space of Swiss mouse fetuses. Nine-day-old embryos were exposed to 2 and 4 μ g ENU and died within the first 4 wk of life. The injection of 4 μ g ENU into 11-day-old fetuses induced a 10% lung tumor incidence, whereas the injection of 16 μ g injected at 12, 15, or 16 days resulted in lung tumor incidences of 42%, 100%, and 84%, respectively. Fifty percent of 16-day fetuses exposed to 64 μ g of ENU died, and a lung tumor incidence of 89% was seen in the survivors. Histologic examination revealed that the tumors were alveogenic adenomas 1-7 mm in diameter. No tumors occurred in two saline-treated control groups. This biologic model could be used for testing chemical alkylating agents similar to ENU. (22 refs)

79-6715 Tissue Differentiation and Susceptibility to Embryonal Tumor Induction by Ethylnitrosourea in the Opossum. (Eng) Jurgelski, W. (Office Health Hazard Assessment

and Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709); Hudson, P.; Falk, H. L. *Natl Cancer Inst Monogr* (51): 123-158; 1979.

In two separate experiments, 532 opossums (*Didelphis virginiana* Kerr) bred in captivity were divided by litter into 10 age groups ranging from 1 day to 16 wk. In the first experiment, animals were given single po doses of approx 100 mg/kg ethylnitrosourea (ENU). In the second study, the same dose was given in four 25 mg/kg increments on alternate days. Controls received phosphate buffered saline (PBS) only. Histological examinations were made after death or sacrifice of the animals. Unilateral intraocular tumors developed in 5/58 animals given ENU between 1-3 wk of age. Four neoplasms were in males. The cells of origin appeared to be the nonpigmented epithelium of the nonsensory retina. The tumors were malignant teratoid medulloepitheliomas. Embryonal tumors of the kidney developed in 66/226 opossums exposed to ENU between birth and 6 wk of age. Probable cells of origin were the nephrogenic and stromatogenic stem cells of the kidney. The renal tumors exhibited characteristics of Wilms' tumor or nephroblastoma. Polycystic kidney was observed in some animals. Brain neoplasms, originating most frequently in the subependymal region of a lateral ventricle, were found in 12/198 animals given single doses of ENU between birth and 56 days of age. The neoplastic cells were neurons, and the tumors were gangliomas. Epithelial odontogenic neoplasms developed in 32/277 animals within 2 mo of ENU exposure. These tumors were analogous to ameloblastomas, and they arose at different stages of development from embryonic teeth, dental remnants, or buccal mucosa. (92 refs)

79-6716 Transplacental Effects of Ethylnitrosourea in a Nonhuman Primate, *Erythrocebus patas*. (Eng) Rice, J. M. (Experimental Pathology Branch, NCI, Bldg. 37, Room 3A09, Bethesda, MD 20205); Sly, D. L.; Palmer, A. E.; London, W. T. *Natl Cancer Inst Monogr* (51): 185-192; 1979.

Erythrocebus patas were established into breeding units of one male and two females. When females became pregnant, they received iv injections of 0.1 millimole (mmol)/kg (12 mg) of ethylnitrosourea (ENU) at 7-14 day intervals for carcinogenesis studies and 1.0 mmol/kg for toxicity studies. To study transplacental passage, a near-term pregnant female was given an iv injection of 0.1 mmol/kg ENU to which 0.68 mCi labeled ENU in 0.10 ml ethanol had been added. Blood samples were taken from the umbilical vein and the saphenous vein of the mother. The fetus was killed 15 min after the mother had received the injection, and tissue samples were removed from the fetus. Thirteen juveniles (four males and nine females) were given 0.1 mmol/kg ENU every 14 days for comparison with progeny exposed to ENU at 30, 50, and 60 days gestation. Repeated doses of ENU, given at 14-day intervals, were tolerated without apparent signs of toxicity by fetal, pregnant, and juvenile monkeys. During the latter two-thirds of pregnancy the interval could be reduced to seven days. Large single doses (1.0 mmol/kg) were tolerated by pregnant females but frequently resulted in abortion. These doses produced acute cytolytic damage to cells of the periventricular germinal matrix of the fetal brain. Studies with labeled ENU showed no placental barrier to this carcinogen. Specific activities were highest in fetal liver. As of December 1975, no tumors had been observed. (27 refs)

79-6717 2,5-Dithiobiurea. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (132): 1-48; 1979.

The carcinogenicity of 2,5-dithiobiurea (DTU), a component of photographic chemicals, was studied in Fischer 344 rats and B6C3F1 mice. DTU was incorporated into the rats' diet at 0.6% or 1.2% for 78 wk, and was added to the diet of the mice at 1.0% or 2.0% for 78 wk. A subchronic feeding study was also conducted. DTU treatment was associated with a decrease in mean body wt in mice but not in rats. No consistent pattern of clinical signs was observed in either species. Tumor incidence was not significantly increased in DTU-treated rats or male mice relative to untreated controls. The incidence of hepatocellular carcinoma increased significantly with dose in DTU-treated female mice and decreased significantly with dose in DTU-treated male mice. It is concluded that under the conditions of this bioassay, DTU is carcinogenic in female B6C3F1 mice but not in male B6C3F1 mice or male or female Fischer 344 rats. (21 refs)

79-6718 Bioassay of 1-Phenyl-2-Thiourea for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (148): 44 pp.; 1979.

1-Phenyl-2-thiourea (PTU) was tested for possible carcinogenicity by administering it in the diet of Fischer 344 rats and B6C3F1 mice at either of two concentrations (120 and 60 ppm for rats, 300 and 150 ppm for mice). Fifty males and 50 females of each species were used in each group with 20 males and females of each species as controls. Treatment resulted in a distinct depression of mean body wt in males and females of each group, but no significant positive association could be established between treatment and tumor incidence. Significantly accelerated mortality or other toxic effects were not observed in treated animals. It is concluded that, under the conditions of the assay, PTU is not carcinogenic to Fischer 344 rats or B6C3F1 rats. (19 refs)

79-6719 Tolazamide. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (51): 1-94; 1979.

The carcinogenicity of tolazamide, an oral hypoglycemic agent, for Fischer 344 rats and B6C3F1 mice was studied. Tolazamide was incorporated in the diet 5 days/wk for 103 wk at 5,000 or 10,000 ppm. Subchronic feeding studies were also conducted to estimate the max tolerated doses of tolazamide. Tolazamide treatment was associated with decreases in mean body wt in both rats and mice, but there were no other clinical signs of toxicity. Survival rates were higher among treated rats than among controls and lower among treated mice than controls. The incidences of C-cell adenomas and carcinomas of the thyroid were nonsignificantly increased in male rats compared with controls. All observed tumors were of types commonly found in the animal strains used, and there were no significant differences in tumor incidence among treated or control animals. It is concluded that under the conditions of this bioassay, tolazamide is not carcinogenic in Fischer 344 rats or in B6C3F1 mice. (14 refs)

79-6720 Acetohexamide. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (50): 1-92; 1979.

The carcinogenicity of dietary acetohexamide (AHA: 10,000 or 20,000 ppm) in Fischer 344 rats and B6C3F1 mice was studied in a

103-wk trial. Subchronic studies were also conducted to estimate the max tolerated doses of AHA. AHA feeding caused a dose-dependent decrease in mean body wt in both mice and rats, but no other clinical signs related to AHA administration were observed. The incidence of leukemia was greater among the AHA-treated rats than among the untreated controls, but the difference was significant only in the case of males given 10,000 ppm AHA. Most leukemias were of the undifferentiated mononuclear cell type, which commonly occurs spontaneously in Fischer 344 rats. Thus, the increased incidence of this disease in AHA-treated rats cannot clearly be associated with its administration. Lymphomas, which commonly occur in untreated B6C3F1 mice, occurred at a non-significantly higher frequency among AHA-treated male mice than among untreated male mice. It is concluded that under the conditions of this bioassay, AHA is not carcinogenic for Fischer 344 rats or B6C3F1 mice. (19 refs)

79-6721 In Vivo Studies in Syrian Golden Hamsters: A Transplacental Bioassay of Ten Nitrosamines. (Eng) Althoff, J. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Grandjean, C. *Natl Cancer Inst Monogr* (51): 251-255; 1979.

The carcinogenic effects of a single low dose of 10 nitrosamines, each administered sc, were determined in pregnant Syrian golden hamsters and their offspring. The compounds studied included dimethylnitrosamine, di-n-propylnitrosamine, di-n-butylnitrosamine, nitrosopiperidine, nitrosohexamethyleneimine, 2-hydroxypropyl-propyl-nitrosamine, methylpropylnitrosamine, di(2-hydroxypropyl)nitrosamine, and 4-hydroxybutyl-butyl-nitrosamine. Tumor incidences of all organ systems were almost always higher and latencies shorter in the mothers than in the offspring. Exceptions occurred in the respiratory system in which several compounds induced a low incidence of tumors in the offspring but none in the mothers. Fetal susceptibility appeared greatest toward the end of gestation. For bioassay purposes, transplacental exposure was less efficient than conventional adult treatment. (16 refs)

79-6722 Intake of Volatile Nitrosamines from Consumption of Alcohols. (Eng) Walker, E. A. (International Agency Res. Cancer, 150 cours Albert-Thomas, 69372, Lyon, Cedex 2, France); Castegnaro, M.; Garren, L.; Toussaint, G.; Kowalski, B. *J Natl Cancer Inst* 63(4): 947-951; 1979.

During epidemiologic studies concerning the relationship between esophageal cancer incidence and alcohol consumption in Normandy, France, volatile nitrosamine levels were determined in alcoholic beverages. Nitrosodimethylamine (NDMA) was found in most alcoholic drinks tested, with the exception of wine. The av level, about 2 µg/liter in beer, was higher than that for other drinks; the range was 0.2-8.6 µg/liter. Traces of nitrosodiethylamine were also detected in spirits and ciders. No significant increases in these levels were found after nitrosation. The calculation of daily alcohol intake in the study region showed that the main intake of volatile nitrosamine is from NDMA in beer. NDEA intake from cider is about one-third that of NDMA from all sources. (18 refs)

79-6723 Mutagenicity and Cytotoxicity of Nineteen Heterocyclic Mustards (ICR Compounds) in Cultured

Mammalian Cells. (Eng) Fuscoe, J. C. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); O'Neill, J. P.; Peck, R. M.; Hsie, A. W. *Cancer Res* 39(12): 4875-4881; 1979.

The mutagenicity and cytotoxicity of 19 ICR compounds, including 6 reported previously, were determined in the Chinese hamster ovary hypoxanthine-guanine phosphoribosyltransferase system. A phenotypic expression time of 9 days was used, based on the 7- to 9-day expression times required for ICR 170 and 191. Thirteen of these compounds were mutagenic. At equimolar concentrations, the compounds with the tertiary amine-type side chain (ICR 217, 340, 355, 368, 170, and 292) were more mutagenic than the compounds with the secondary amine-type side chain (ICR 449, 371, 191, and 372). All secondary amine types reached a "plateau" in their concentration-dependent mutagenesis curves at 3 to 4 μ M. Shortening of the side chain by one carbon (ICR 171) reduced mutagenicity. Substitution of a sulfur atom for a nitrogen in the side chain (ICR 342) increased both mutagenicity and cytotoxicity. The presence of two 2-chloroethyl groups on the side chain (ICR 220) resulted in greatly increased cytotoxicity and mutagenicity. With the 2-chloroethyl group of ICR 340, 372, 292, 191, or 170 replaced by a 2-hydroxyethyl group (ICR 340-OH, 372-OH, 292-OH, 191-OH, or 170-OH), a mutagenically inactive compound resulted which nevertheless remained toxic. Replacement of the amine linkage with an ether linkage (ICR 283) also yielded a mutagenically inactive compound. (18 refs)

79-6724 Effect of Chronic N,N-Diethylnitrosamine on the Excision of O⁶-Ethylguanine from Rat Liver DNA. (Eng) Margison, G. P. (Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Curtin, N. J.; Snell, K.; Craig, A. W. *Br J Cancer* 40(5): 810-814; 1979.

The effect of N,N-diethylnitrosamine (DEN: approx 10 mg/kg/day in drinking water for 5 or 10 wk) on the excision of O⁶-ethylguanine (O-EG) from the liver DNA of male Wistar rats was studied. The levels of 7-ethylguanine (7-EG) and 3-ethyladenine (3-EA) in the liver DNA of the rats given DEN for 5 wk (5-wk group) were higher than in untreated controls, and the 3-EA:7-EG ratio was decreased by 6% in the 5-wk group. 3-EA and 7-EG levels were slightly lower in the 10-wk group than in controls, and the ratio of 3-EA:7-EG was 6% higher in controls. The levels of O-EG were reduced by 60% and 90% in the 5-wk and 10-wk groups, respectively, compared with the control rats. The O-EG:7-EG ratios were 26% and 7% of the control values in the 5-wk and 10-wk groups, respectively. (24 refs)

79-6725 Tissue Differentiation as a Prerequisite for Transplacental Carcinogenesis in the Hamster Respiratory System, with Specific Respect to the Trachea. (Eng) Mohr, U. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Reznik-Schuller, H.; Emura, M. *Natl Cancer Inst Monogr* (51): 117-122; 1979.

Female Syrian golden hamsters (15 groups of six) were given a single sc injection of 45 mg diethylnitrosamine (DEN)/kg on one of the 15 days of pregnancy. An equivalent group treated on day 15 with the solvent (physiologic saline) alone served as a vehicle control. Both mothers and offspring surviving the weaning period were observed until spontaneous death. At autopsy, histological and ultrastructural studies were performed on sections of larynx

and trachea. In another experiment, 74 female Syrian golden hamsters were killed on each of the different days of pregnancy, and fetal trachea with lungs were excised and studied as in the experiment. Offspring of mothers receiving DEN on one of the first 11 days of pregnancy developed no respiratory tract tumors. A pronounced neoplastic response was found in young from mothers treated on one of the last four days of pregnancy. The tumor incidence increased to 95% in those animals treated on the 15th prenatal day. Most of the neoplasms were in the larynx and trachea; only a few were found in the nasal cavities and lungs. Mothers also showed a high incidence of tracheal and laryngeal tumors. These tumors were papillomas and papillary polyps. Nasal cavity tumors were adenocarcinomas and squamous cell carcinomas. All pulmonary tumors were bronchogenic adenomas. In the second experiment, histological examination revealed that the trachea separates from the embryonal esophagus between the 9th and 10th prenatal days. The largest number of mitotic figures were found on the 11th day. Since max carcinogenic effect of DEN was observed between days 12 and 15, carcinogenic and mitotic activity did not appear to be directly related. Electron microscopy revealed that cells were still poorly differentiated up to the 12th day of gestation. Beginning with the 12th day, a progressive condensation of heterochromatin was observed, and the first rough endoplasmic reticulum (RER) appeared. Since DEN requires conversion to its ultimate carcinogen before exhibiting carcinogenic effects, it was concluded that this process depended on appearance of the RER, which is known to bear the nonspecific enzymes needed for DEN conversion. (13 refs)

79-6726 Metabolism of Three Radiolabeled Pancreatic Carcinogenic Nitrosamines in Hamsters and Rats. (Eng) Gingell, R. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE 68105); Brunk, G.; Nagel, D.; Pour, P. *Cancer Res* 39(11): 4579-4583; 1979.

The in vivo metabolism and disposition of three radiolabeled N-nitrosamines which are carcinogenic for the pancreas of the hamster but not the rat have been examined. N-[1-¹⁴C]Nitrosobis(2-oxopropyl) amine (BOP), N-[1-¹⁴C]Nitrosobis(2-hydroxypropyl)amine (BHP), and their suggested proximate pancreatic carcinogenic metabolite N-[1-¹⁴C] nitroso-(2-hydroxypropyl) (2-oxopropyl)amine (HPOP) were administered ip to male Syrian hamsters or Wistar rats in doses of 10 or 100 mg/kg. The carcinogens were metabolized and exhaled as ¹⁴CO₂ to various extents somewhat proportional to their carcinogenic potency. More than 50% of the dose of BOP and HPOP was exhaled as ¹⁴CO₂; only 26% of the BHP dose was thus excreted, while 40% of it was excreted unchanged in the urine. Administered BOP was excreted to a small extent in the urine of both species as HPOP and BHP. No other nitrosamine metabolites were detected in urine. HPOP and BHP were detected in the pancreatic juice and bile of both species after administration of BOP and BHP. The results suggest that pancreatic ductular carcinogenesis in the hamster as a result of exposure to BOP is not due to secretion of carcinogenic metabolites in the pancreatic juice or reflux of bile containing nitrosamine metabolites into the ducts. Metabolic activation of the carcinogen(s) appears to be by an oxidative pathway. (25 refs)

79-6727 Experimentally Induced Pancreas Carcinoma After Choledochojunostomy. (Ger) Ruckert, K. (Chirurgische Universitätsklinik, Langenbeckstrasse 1, D-6500 Mainz, W. Germany); Klink, E.; Kloppel, G. *Langenbecks Arch Chir* 348(4): 261-268; 1979.

The significance of bile reflux in the development of pancreatic carcinoma after exposure to chemical carcinogens was tested in Syrian golden hamsters. Female hamsters (9 wk old) were given dihydroxy-di-n-propylnitrosamine (DHPN, 125 mg/kg body wt) for 15 wk via different routes. Two groups underwent choledochojejunostomy before DHPN in olive oil was injected sc (group 3) or given by stomach tube (group 4). In group 3, 1/20 hamsters had a pancreatic carcinoma and 6 had precancerous changes in the pancreas. One carcinoma and 3 hamsters with precancerous changes were found among 15 animals in group 4. In group 1 (DHPN sc, no surgery) 4/17 carcinomas (all in the body or tail of the pancreas) and 12 hamsters with precancerous lesions were found. In group 2 (DHPN by stomach tube, no surgery) carcinomas of the pancreatic head were seen in 9/16 animals, and 13 hamsters had precancerous changes. No cancerous or precancerous changes were found in the untreated or surgery-only control groups. These data indicate that the bile is a carrier of nitrosamines and a factor in the development of pancreatic carcinoma. (11 refs)

- 79-6728 The Morphologic and Biologic Patterns of Chemically Induced Pancreatic Adenocarcinoma in Syrian Golden Hamsters After Homologous Transplantation. (Eng) Takahashi, M. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE 68105); Runge, R.; Donnelly, T.; Pour, P. *Cancer Lett* 7(2/3): 127-133; 1979.

A pancreatic adenocarcinoma induced by N-nitrosobis(2-oxopropyl)amine (2.5 mg/kg body wt, injected sc 1x/wk for 20 wk) in the Syrian golden hamster was successfully transplanted to a homologous host by sc inoculation through 10 successive passages. The rate of tumor take increased progressively with each generation from 60% to 100%, while the latency period after inoculation was reduced simultaneously from 6 wk to 1 wk in the second and following passages. The tumors grew rapidly, ulcerated the overlying skin, and metastasized to the regional lymph nodes and lungs. Most animals died with multiple lung metastases between the 5th and 20th wk. All transplanted tumors and their metastases retained the pattern of the original well-differentiated adenocarcinomas. (12 refs)

- 79-6729 Determination of Volatile Nitrosamines in Crops and Soils Treated with Dinitroaniline Herbicides. (Eng) West, S. D. (Lilly Res. Lab., Div. Eli Lilly and Company, Greenfield, IN 46140); Day, E. W. *J Agric Food Chem* 27(5): 1075-1080; 1979.

Solvent extraction procedures were developed for the routine determination of the volatile nitrosamines N-nitrosodi-n-propylamine (NDPA) and N-nitroso-N-n-butyl-N-ethylamine in crops, soils, and water. Plant tissue was extracted with methanol and soil with methanol/water (3:1). The extracts were purified by liquid-liquid extraction and alumina column chromatography, and residues were measured by gas chromatography-thermal energy analysis. The sensitivity of the method was 0.2, 0.05, and 0.01 ppb for NDPA in crops, soils, and water, respectively. No detectable nitrosamines were observed in crops treated with the herbicides trifluralin, benefin, or oryzalin. (24 refs)

- 79-6730 p-Nitrosodiphenylamine. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (190): 1-49; 1979.

The carcinogenicity of p-nitrosodiphenylamine (NDPA), a vulcanization accelerator and chemical intermediate, was studied in Fischer 344 rats and B6C3F1 mice. NDPA was added to the rats' diet at 2,500 or 5,000 ppm for 78 wk; for mice, the dose was 5,000 ppm for 40 wk followed by 2,500 ppm for 17 wk, or 10,000 ppm for 40 wk followed by 0 ppm for 7 wk followed by 5,000 ppm for 10 wk. Subchronic feeding studies were also conducted. In mice but not rats, mortality was significantly associated with NDPA dose. Dose-related decreases in body wt were observed among treated rats. In male rats, the incidence of hepatocellular carcinomas and neoplastic liver nodules increased significantly with NDPA dose, and there was also a positive association between drug dose and the incidence of alveolar/bronchiolar adenomas. The latter finding was of questionable significance. Tumor incidence was not significantly increased in NDPA-treated female rats or female mice. The incidence of hepatocellular carcinomas was significantly higher among male mice given the lower doses of NDPA than among their controls. It is concluded that under the conditions of this bioassay, NDPA is carcinogenic in male B6C3F1 mice and male Fischer 344 rats, but not in females of either species. (18 refs)

- 79-6731 A Technique for Multiparametric Analysis of Hemodynamic Changes in Rat Urinary Bladder During Carcinogenesis by N-Butyl-N-(4-hydroxybutyl)nitrosamine. (Eng) Lurie, A. G. (Dept. Oral Diagnosis, Div. Oral Radiology, Univ. Connecticut Health Center, Farmington, CT 06032); Rippey, R. M.; Conran, P. B.; Tatematsu, M.; Ito, N. *Gann* 70(5): 717-718; 1979.

A technique was developed for the simultaneous study of histopathology and vascular volume, permeability, and perfusion in rat urinary bladder during experimental carcinogenesis. Male Wistar rats received 0.05% N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in the drinking water for 8 wk and were sacrificed 2-40 wk after the start of BBN treatment. At sacrifice, each rat received an injection of rat blood labeled with ^{51}Cr and ^{125}I -human serum albumin (HSA) iv and $^{86}\text{RbCl}$ iv 1 hr later. The bladder was excised 90 sec after RbCl injection. Fractional distributions of ^{51}Cr -RBC, ^{125}I -HSA, and $^{86}\text{RbCl}$ were used to determine vascular volume, permeability, and perfusion, respectively. At wk 2, there was a diffuse epithelial hyperplasia. By wk 20, marked papillary hyperplasia was observed, and transitional cell carcinoma occupied the entire bladder lumen by wk 40. Bladder vascular volume, permeability, and perfusion increased initially, peaking at 2-8 wk. Perfusion remained at this level, while volume and permeability decreased sharply after termination of BBN treatment. Volume then increased from 20 to 35 wk, and permeability increased from 30 to 35 wk. Early increases in vascular volume and permeability may be due to neovascularization secondary to the effect of BBN. Late increases probably represent vascular responses to secretion of an angiogenesis factor from malignant cells. The sustained increase in vascular perfusion suggests the existence of alterations in transendothelial nutrient movement caused by BBN. (5 refs)

- 79-6732 Mutagenic and DNA-damaging Effects of N-Alkyl-N-(α -acetoxyalkyl) nitrosamines, Models for Metabolically Activated N,N-Dialkylnitrosamines. (Eng) Mochizuki, M. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan); Suzuki, E.; Anjo, T.; Wakabayashi, Y.; Okada, M. *Gann* 70(5): 663-670; 1979.

Mutagenic and DNA-damaging effects of a series of N,N-dialkylnitrosamines monosubstituted at the α -carbon with an acetoxy group were tested in *Salmonella typhimurium*, *Escherichia coli*, and *Bacillus subtilis* in the absence of metabolic activation. The compounds included eight N-alkyl-N-(acetoxymethyl)nitrosamines (alkyl = methyl, ethyl, propyl, isopropyl, *sec*-butyl, or *tert*-butyl) and N-butyl-N-(1-acetoxybutyl)nitrosamine. All the compounds except that with a *tert*-butyl group gave positive results in all tests. Presumed release of alkyl cations from the corresponding α -acetoxy derivatives by hydrolysis and heterolysis caused mutagenic and DNA-damaging effects in the bacteria. Structure-activity correlation of the compounds was noted in these tests and discussed in regard to the mutagenicity with metabolic activation and the carcinogenicity of N,N-dialkylnitrosamines. The results support the hypothesis that α -carbon hydroxylation is one probable mechanism involved in the metabolic activation of N,N-dialkylnitrosamines. (35 refs)

- 79-6733 Development of Urinary Bladder Cancer in the Rat. (Eng) Kunze, E. (Pathologisches Institut der Universität, Gosslerstrasse 10, 3400 Gottingen, W. Germany). *Curr Top Pathol* 67: 145-232; 1979.

Morphological, enzyme histochemical, and autoradiographic methods were used to study carcinogenesis in the bladder mucosa of the rat following the application of the carcinogens di-N-butylnitrosamine, N-butyl-N-(4-hydroxybutyl)-nitrosamine, and N[4-nitro-2-furyl]-2-thiazolylformamide. Transitional cell carcinomas developed mainly through successive stages of transformation. The first stage consisted of a focal irreversible loss of alkaline phosphatase activity in histologically and cytologically normal urothelium. These areas were considered to be preneoplastic in that papillomas developed from such areas via enzyme-deficient hyperplasias after marked proliferative activity of enzyme-deficient urothelial cells. Most papillomas and carcinomas also showed a loss of alkaline phosphatase activity. Most carcinomas developed by way of malignant transformation of preexisting papillomas or their precursors, the papillary hyperplasias. The transition into focally malignant growth occurred in a stepwise manner through different successive stages of transformation. These stages consisted of a focal, sharply defined cellular atypia, followed by the development of carcinomas *in situ* and then by circumscript infiltrative growth. After transformation was initiated at the molecular level, the successive development of each stage occurred independently of further carcinogen treatment. The number of papillomas with transformation stages increased with the length of exposure and induction time, but these factors had no influence on proliferative activity. Transitional cell carcinomas usually developed from papillomas, but they seldom developed from primary carcinomas *in situ*. The spectrum of carcinomas induced included all types known to occur in humans. The adenocarcinomas originated from glandular metaplasia, and the squamous carcinomas developed from squamous metaplasia within completely developed transitional cell carcinomas. (125 refs)

- 79-6734 Analysis of Nitrosamines in Aqueous and Biological Fluids Based on Measurement of Photochemically Liberated Nitrite. (Eng) Musson, D. G. (Dept. Pharmaceutical Chemistry, Univ. Kansas, Lawrence, KS 66045); Sternson, L. A. *J Pharm Sci* 68(9): 1159-1162; 1979.

A method for the analysis of nitrosamines in aqueous solution and in blood, plasma, and rat liver microsomal suspensions is

described. N-nitrosopyrrolidine, N-nitrosodimethylamine, and N,N-diethanolnitrosamine were used as model compounds. The method is based on photochemical degradation of the nitrosamine in a controlled environment to yield the corresponding amine and nitrite ion, and the latter is subsequently used to form a chromophoric or fluorescent product. The analysis scheme is a modular three-component system consisting of a column to remove contaminating nitrite prior to photolysis, a photochemical reactor, and a chemical reactor. Additional modules are used to accommodate biological samples or large-volume (5-50 ml) aqueous samples. Because of intersubstrate variability in the photochemical decomposition rate and overall nitrite yield, the structure (ie, photochemical behavior) of the particular nitrosamine in the samples must be known prior to analysis. With a colorimetric readout, the sensitivity for analysis of N-nitrosopyrrolidine was 800 ng/ml for a 5-ml sample, and the measurement precision was $\pm 6\%$ in the biological fluids. Fluorometric analysis improved sensitivity to 4 ng/ml with a precision of $\pm 10\%$ in biological media. (18 refs)

- 79-6735 An Investigation into the Cytogenetic Damage Induced by the Coccidiostatic Agents Amprolium, Carbadox, Dimetridazole and Ronidazole. (Eng) Oud, J. L. (Dept. Cytogenetics and Population Genetics, Inst. Genetics, Univ. Amsterdam, Kruislaan 318, 1098 SM Amsterdam, Netherlands); Reutlinger, A. H.; Branger, J. *Mutat Res* 68(2): 179-182; 1979.

The mutagenicity of amprolium, dimetridazole, and ronidazole (coccidiostatic agents added to poultry feed, and carbadox (added to pig feed) were studied. Of the four agents, only carbadox (52.5-525 mg/kg) induced significant numbers of micronucleated polychromatic RBC in male and female mice following a single ip injection. Carbadox (210 mg/kg) also significantly increased the number of chromatid aberrations in mice 24-36 hr following a single ip dose; the maximal effect was observed 30 hr after treatment. Further investigations concerning the clastogenic potential of carbadox are warranted. (8 refs)

- 79-6736 Carcinogenicity of N-Nitroso-Ethylenethiourea in Female Mice. (Eng) Moriya, M. (Inst. Environmental Toxicology, Suzuki-cho 2-772, Kodaira-shi, Tokyo 187, Japan); Mitsumori, K.; Kato, K.; Miyazawa, T.; Shirasu, Y. *Cancer Lett* 7(6): 339-342; 1979.

Groups of 20 outbred ICR female mice (5 wk old) received N-nitroso-ethylenethiourea (N-nitroso-ETU: 0.66, 1.32, or 2.64 mg/wk \times 10, po) and were observed for 53 wk after the first dose. There was a significant increase in the number of mice with pulmonary and lymphocytic neoplasms; the incidence of these tumors appeared to be dose-dependent. There were no lung tumors in control mice compared with 4/20, 5/19, and 10/19 in groups given 0.66, 1.32, and 2.64 mg N-nitroso-ETU, respectively. There were no lymphocytic neoplasms in the control mice, but 2/20, 5/19, and 5/19 mice given 0.66, 1.32, and 2.64 mg of the test compound, respectively, developed such tumors. One control mouse and one mouse from the highest dosage group developed reticulum cell neoplasms. The higher dosage groups also developed tumors earlier than did the lower dosage groups. The results indicate that N-nitroso-ETU is carcinogenic in the lung and lymphoreticular system. (6 refs)

- 79-6737 In Vitro Transformation of Hamster Embryo Cells with a Glutamic Acid Pyrolysis Product. (Eng)

Takayama, S. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Hirakawa, T.; Tanaka, M.; Kawachi, T.; Sugimura, T. *Toxicol Lett* 4(4): 281-284; 1979.

The activity of the glutamic acid pyrolysis product 2-amino-6-methyldiprido[1, 2-a:3',2'-d]imidazole (Glu-P-1) was studied in vitro in a transformation assay with cryopreserved hamster embryo cells. Glu-P-1 was cytotoxic at a concentration of 50 µg/ml but induced morphological transformation of the cells at concentrations of 10 and 20 µg/ml. Glu-P-1 may be carcinogenic for experimental animals. (8 refs)

79-6738 Squamous-Cell Carcinoma Arising in a Basal-Cell Epithelioma Treated with 5-Fluorouracil. (Eng) Kurtis, B. (Dept. Dermatology, Veterans Admin. Hosp., Houston, TX); Rosen, T. *J Dermatol Surg Oncol* 5(5): 394-396; 1979.

The development of a squamous cell carcinoma within a basal cell epithelioma of a 33-yr-old man treated with 5-fluorouracil (5-FU: 800 mg instilled intralesionally over a 6-wk period) is reported. It is concluded that 5-FU may, in exceptional instances, precipitate the development of squamous cell carcinoma within or upon a preexisting basal cell epithelioma. Thus, this form of treatment cannot be recommended. (8 refs)

79-6739 Identification of S-(Carboxymethyl)-L-Cysteine and Thiodiglycolic Acid, Urinary Metabolites of 2,2'-Bis-(Chloroethyl)-Ether in the Rat. (Eng) Muller, G. (Institut für Staublungenforschung, Arbeitsmedizin, Universität Munster, Munster, W. Germany); Norpoth, K. *Cancer Lett* 7(5): 299-305; 1979.

The metabolism of the hepatocarcinogen 2,2'-bis-(chloroethyl)-ether (BCEE) was studied following ip injection (100 mg/kg body wt) in male SPF Wistar rats. S-(carboxymethyl)-L-cysteine (CMC) and thiodiglycolic acid (TGA) were identified by gas chromatographic-mass spectrometric measurements in the urine of BCEE-treated rats. It is therefore probable that BCEE is O-dealkylated by a mixed-function oxidation. The hepatocarcinogenic effect of BCEE may be explained by the liberation of chloroacetaldehyde in vivo, at TGA and CMC are metabolites of the latter chemical. (23 refs)

79-6740 Selectivity in Nucleoside Alkylation and Aalkylation in Relation to Chemical Carcinogenesis. (Eng) Moschel, R. C. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Hudgins, W. R.; Dipple, A. *J Org Chem* 44(19): 3324-3328; 1979.

The sites of benzylation of adenosine and guanosine by different benzylating agents were investigated to elucidate those properties of chemical reactivity that determine sites of reaction on nucleic acid constituents. The differences in chemical reactivity associated with reaction at ring nitrogen atoms as opposed to exocyclic sites were investigated by studying benzylation in different solvent systems. The differences in chemical reactivity associated with a preference for either the exocyclic O⁶ or N² positions in guanosine were investigated using benzylating agents with different leaving groups. The more aqueous solvents specifically promoted reaction on the exocyclic amino group in both the adenosine and guanosine

studies. The effects of the different leaving groups examined were such that the yield of ring-substituted product was always greater for the bromide than for the chloride, and that for the chloride was greater than that for the tosylate. With exocyclic substitution, yields were always lower for the chloride than for the bromide and tosylate. Exocyclic substitution for the tosylate was greater than that for the bromide in 20%-60% organic solvent in water but was less than that for bromide in the most aqueous solvent. Since potent carcinogens are found among agents that modify the O⁶ site on guanine residues and also among those that modify the N² site on guanine residues, the results suggest that a limited dependence on or susceptibility to, nucleophilicity is enough to render a reactive chemical potentially carcinogenic. (37 refs)

79-6741 Bioassay of Methyl Parathion for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (157): 112 pp.; 1979.

Methyl parathion was tested for possible carcinogenicity in F344 rats and B6C3F1 mice. Groups of 50 rats or mice of each sex received the test chemical in feed at one of two concentrations (20 or 40 ppm for rats; 62.5 or 125 ppm for female mice and for male mice initially; doses reduced to 20 and 50 ppm for male mice on wk 37, due to excessive wt loss) for 105 wk (rats) or 102 wk (mice). Groups of matched animals fed a normal diet were used as controls. Mean body wt in rats and mice of both sexes were significantly lower than those of controls throughout the assay. No correlation between treatment and survival (except for an increased mortality in the high-dose female rats) or between treatment and tumor incidence were observed. It is concluded that, under the conditions of the assay, methyl parathion is not carcinogenic in F344 rats and B6C3F1 mice of either sex. (22 refs)

79-6742 Reactions of N-Methyl-N-Nitrosobenzylamine and Related Substrates with Enzyme-containing Cell Fractions Isolated from Various Organs of Rats and Mice. (Eng) Schweinsberg, F. (Hygiene-Institut der Universität, Silchesterstr. 7, D-7400 Tübingen, W. Germany). *Cancer Lett* 7(2/3): 115-120; 1979.

The metabolism of N-methyl-N-nitrosobenzylamine (MNBA), N-methyl-N-nitroso-(α -phenyl)-ethylamine (MNPE), and N-methyl-N-nitroso-(2-phenyl)-isopropylamine (MNPI) was studied in microsomes isolated from various organs of female SIV 50 rats and NMRI mice. The metabolites were identified by gas chromatograph-mass spectrometry and high pressure liquid chromatography. The reaction of MNBA with mouse liver microsomes yielded benzaldehyde; MNPE yielded formaldehyde and acetophenone; and MNPI gave formaldehyde. The same qualitative results were obtained with microsomes of rat liver, rat esophagus, and mouse forestomach; but mouse liver microsomes generated more benzaldehyde from MNBA than did rat liver microsomes. Pretreatment of the mice with 0.1% phenobarbitone in the drinking water for 5 days increased the formation of benzaldehyde by a factor of 2. Microsomes from the rat organs showed decreasing activity in the sequence esophagus > forestomach > liver; for the mice the sequence was liver > forestomach. These results provide evidence that nitrosamine metabolism in rodents occurs through the oxidation of a C atom adjacent to the nitrogen function. The results, however, do not help to reconcile the metabolic findings and enzyme activities with the established tissue and species specificities for the carcinogenicity of the compounds investigated. (7 refs)

79-6743 Nucleic Acid Base and Carcinogen Metabolite Specificities During Intercalative Interactions Between DNA and 4-Nitroquinoline-1-Oxide. (Eng) Ornstein, R. L. (Dept. Biochemical Sciences, Frick Lab., Princeton Univ., Princeton, NJ 08540); Rein, R. *Chem Biol Interact* 27(2/3): 291-311; 1979.

The biophysical properties of the intercalative interactions occurring between 4-nitroquinoline-1-oxide (4NQO) and its metabolites with DNA minihelices were studied. The initial intercalated-complex models were energy-minimized to obtain the favored geometrical arrangement for each of seven 4NQO metabolites (NO_2 , NO_2^- , N=O , NOH , NHOH , NH_2 , or NH^+ substituted at the 4-position of quinoline) in each of several different minihelices, and the energies were determined using the expanded-optimized empirical-potential method. The results indicate that intercalation of 4NQO or its metabolic intermediate forms probably precedes the covalent bond formation of the ultimate carcinogenic form with the DNA. The various intercalated quinoline metabolites do not generally enter into "strictly" parallel-planar stacked orientation. Intercalation is energetically permitted for six of seven metabolites studied, although intercalation into $\text{Pyr}(3'-5')\text{Pur}$ sequences is favored over $\text{Pur}(3'-5')\text{Pyr}$ sequences. The three metabolites that are more energetically favored to enter intercalation (NH^+ , NH_2 , N=O), are also known to enter into the greatest amount of covalent binding with DNA and its constituents, suggesting a two-step binding mechanism (intercalation followed by covalent binding). (42 refs)

79-6744 An In Vitro Chromosome Assay Using Cultured Rat-Liver Cells. (Eng) Dean, B. J. (Shell Res. Ltd., Shell Toxicology Lab., Sittingbourne, Kent ME9 8AG, England); Hodson-Walker, G. *Mutat Res* 64(5): 329-337; 1979.

An in vitro chromosome assay is presented which utilizes an epithelial-like cell line derived from rat liver. The cell line, designated RL₁, retains sufficient metabolic enzyme activity to detect chromosome damage induced by a variety of chemical mutagens and carcinogens without the incorporation of an extrinsic metabolizing system. The cells are grown on standard glass microscope slides, exposed to the test chemical, and processed in situ for metaphase analysis. In a small validation study, chromosome damage was detected in cultures exposed to the direct-acting agents methyl nitronitrosoguanine, 4-nitroquinoline-N-oxide, propylene oxide, epichlorohydrin, and 1,2:3,4-diepoxybutane and to compounds requiring metabolic activation, including cyclophosphamide, 2-acetylaminofluorene, 3-methylcholanthrene, and 7,12-dimethylbenz[a]anthracene. Negative results were obtained with pyrene and carbon tetrachloride. (6 refs)

79-6745 Isolation of Gram Quantities of Configurational Isomers of Cyclic Nitrosamines by Preparative Liquid Chromatography. (Eng) Singer, S. S. (Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD); Singer, G. M. *J Liq Chromatogr* 2(8): 1219-1228; 1979.

Two substituted cyclic nitrosamines, 2,6-dimethyl-N-nitrosomorpholine and 3,5-dimethyl-N-nitrosopiperidine, were separated into their component configurational isomers by preparative high-pressure liquid chromatography (HPLC). The use of HPLC made possible the collection of gram quantities of the materials, suitable for animal testing; this method made the isolation more rapid and

much easier than does the conventional open column chromatography method. (6 refs)

79-6746 Hepatic Microsomal Epoxidation of Bromobenzene to Phenols and Its Toxicological Implication. (Eng) Lau, S. S. (Dept. Pharmacology, Univ. Michigan Medical Sch., Ann Arbor, MI 48109); Zannoni, V. G. *Toxicol Appl Pharmacol* 50(2): 309-318; 1979.

The in vitro epoxidation of bromobenzene by liver microsomes from male Sprague-Dawley rats pretreated with phenobarbital (50 mg/kg/day, ip, for 5 days) was studied. Enzymatic analysis and gas chromatography showed the formation of o-bromophenol via bromobenzene-2,3-epoxide and the formation of p-bromophenol via bromobenzene-3,4-epoxide. Phenobarbital pretreatment caused significant increases in both pathways, whereas pretreatment with 3-methylcholanthrene or β -naphthoflavone caused a marked increase only in the 2,3-epoxide pathway. Multiple forms of cytochrome P-450 were responsible for the formation of o-bromophenol and p-bromophenol. (24 refs)

79-6747 2,4,6-Trichlorophenol. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (155): 1-115; 1979.

The carcinogenicity of dietary 2,4,6-trichlorophenol was tested in 6-wk-old F344 rats and B6C3F₁ mice. The rats and male mice were fed the test chemical at 5,000 or 10,000 ppm for 105-107 wk. The female mice received 10,000 or 20,000 ppm for 38 wk and 2,500 ppm or 5,000 ppm for an additional 67 wk. In male rats, lymphomas or leukemias occurred at incidences that were dose-related and were significantly higher in the groups that received the low and high doses than in the controls (4/20, 25/50 and 29/50 in control, low-, and high-dose groups, respectively). The incidence of leukemia was similar in experimental female rats and controls. However, leukocytosis and monocytosis of the peripheral blood and bone marrow hyperplasia occurred in the experimental female rats but not in the controls. In male and female mice, the incidence of hepatocellular carcinomas and of adenomas was significantly increased in the low- and high-dose groups compared with controls and was dose-related (4/20, 32/49 and 39/47 in control, low-, and high-dose males, respectively, and 1/20, 12/50, and 24/48 in control, low- and high-dose females). It is concluded that 2,4,6-trichlorophenol induces lymphomas and leukemias in male F344 rats and induces hepatocellular carcinomas and adenomas in both sexes of B6C3F₁ mice. (21 refs)

79-6748 Transplacental and Lactational Carcinogenesis by Safrole. (Eng) Vesselinovich, S. D. (Dept. Pathology, Pritzker Sch. Medicine, Chicago, IL 60637); Rao, K. V.; Mihailovich, N. *Cancer Res* 39(11): 4378-4380; 1979.

The carcinogenicity of safrole was investigated in (C57BL/6J x C3HeB/FeJ)F₁ fetal and neonatal mice by intragastric administration of the agent to pregnant and lactating C57BL/6J females. Safrole (each treatment 120 $\mu\text{g/g}$ body wt) was administered to (a) pregnant mice (4 times on days 12, 14, 16, and 18 of gestation); (b) lactating mothers (12 times every second day following parturition); or (c) 4-wk-old offspring (180 times: 2x/wk for 90 wk). Two additional groups of offspring received a, b, and a, b, and c combination treatments. All survivors were killed at 94 wk of age. Renal epithelial tumors were observed in 7% of female offspring

exposed to safrole in utero; none of the other experimental and control animals developed these tumors. Only male offspring nursed by mothers treated with safrole developed hepatocellular tumors (34%). In contrast, direct administration of safrole, beginning at the time of weaning and continuing for the duration of the experiment, led to a significantly high incidence of hepatocellular tumors in females (48%), but not in males (8%). Of the liver tumors observed in females, 86% were hepatocellular carcinomas with a high rate of pulmonary metastases (42%). The data suggest that safrole or its metabolites came into contact with fetuses by crossing the placenta and with infants through its excretion in milk to exert the perinatal carcinogenicity. (56 refs)

79-6749 Dimethyl Terephthalate. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (121): 1-120; 1979.

The carcinogenicity of dimethyl terephthalate was assayed by feeding it at 2,500 or 5,000 ppm to B6C3F1 mice (8 wk old) and F344 rats (7 wk old) in a diet containing 2% corn oil for 103 wk. The animals (50 males and 50 females at each dose) were observed for 104-106 wk. There was no appreciable effect of terephthalate on body wt or on survival in any of the groups. In rats, tumor incidence was significantly higher in experimental groups than in control groups. In male mice, alveolar/bronchiolar adenomas or carcinomas occurred at incidences that were dose-related (1/49 controls, 8/49 low-dose, and 13/49 high-dose groups); in direct comparisons, the incidences were significantly higher in the experimental than in the control group. However, the incidence of alveolar/bronchiolar adenomas and carcinomas and their variability in three other concurrent control groups were such that it could not be concluded that the incidence of these tumors in the experimental group was related to dimethyl terephthalate administration. Twenty-seven of 49 female mice given the high dose developed malignant lymphoma, compared with 16/48 control females. However, the occurrence of lymphomas in aged female B6C3F1 mice is quite variable, and it appears unlikely that this increased incidence is related to dimethyl terephthalate administration. There was a significant negative trend in the incidence of hepatocellular carcinoma in female mice. It is concluded that dimethyl terephthalate is not carcinogenic for F344 rats or B6C3F1 mice under the conditions of this bioassay. (19 refs)

79-6750 Procarbazine. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (19): 1-124; 1979.

The carcinogenicity of procarbazine for B6C3F1 mice and Sprague-Dawley rats was studied in a 52-wk trial. The compound was administered at 6 or 12 mg/kg in mice and 15 or 30 mg/kg in rats (ip, tid). PC administration was associated with decreased mean body wt in the rats and with decreased survival in both species. Tumors involving the epithelial and neuroepithelial tissues of the nasal cavity and turbinates were observed in 21/60 male and 20/59 female rats given PC and in none of the untreated control rats. Olfactory neuroblastomas were significantly more common in PC-treated than in untreated rats. The incidence of malignant lymphomas was also significantly increased in rats given 30 mg/kg PC compared with controls, and mammary adenocarcinomas were significantly more common in PC-treated males and females than in controls. Several other neoplastic and nonneoplastic lesions were also observed in the mammary glands of male and female rats. Several types of squamous cell tumors of the ear canal and

Zymbal's gland were found in increased numbers among the PC-treated rats. Tumors of the epithelial or neuroepithelium of the olfactory bulbs and mucosa were found in 10 male and 11 female mice given 12 mg/kg PC. The incidence of olfactory neuroblastomas was significantly higher in these mice than in the controls. The incidence of leukemia was significantly higher in female mice given 6 mg/kg PC than in controls, uterine adenocarcinomas were significantly more common in PC-treated female mice than in controls, and alveolar/bronchiolar adenomas were significantly more common in PC-treated mice than in controls. Thus, procabazine is carcinogenic in both Sprague-Dawley rats and B6C3F1 mice. (21 refs)

79-6751 5-Chloro-o-toluidine. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (187): 1-44; 1979.

The carcinogenicity of 5-chloro-o-toluidine (5-chloro-2-methylbenzenamine) was tested in 6-wk-old Fischer 344 rats and B6C3F1 mice. The rats were fed diets containing 2,500 and 5,000 ppm and the mice 2,000 and 4,000 ppm 5-chloro-o-toluidine for 78 wk and were observed for an additional 26 wk. The Cochran-Armitage test indicated a significant positive association between the concentration of 5-chloro-o-toluidine given to male rats and the incidence of adrenal pheochromocytomas ($p = 0.019$), but Fisher exact statistical tests did not. In mice of both sexes, there were significant positive associations between the concentration administered and the incidence of hemangiosarcomas (1/20, 11/50, and 37/48 in the control, low-, and high-dose males, respectively, and 0/20, 6/50, and 22/43 in the control, low-, and high-dose females) and hepatocellular carcinomas (4/20, 19/50, and 25/47 in the control, low-, and high-dose males, respectively, and 0/20, 19/50, and 26/43 in the control, low-, and high-dose females). It is concluded that 5-chloro-o-toluidine is carcinogenic in male and female B6C3F1 mice, but there is no conclusive evidence for its carcinogenicity in Fischer 344 rats. (18 refs)

79-6752 o-Toluidine Hydrochloride. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (153): 1-132; 1979.

The carcinogenicity of o-toluidine hydrochloride (THC), an intermediate used in the production of textile dyes, was studied in F344 rats and B6C3F1 mice. THC was incorporated into the diet at a level of 3,000 or 6,000 ppm for 104 wk. Subchronic feeding studies were also conducted to estimate the max tolerated doses of THC. THC feeding was associated with dose-dependent decreases in body wt in both rats and mice and dose-dependent increases in mortality rate in the rats. The incidences of the following tumors were increased in THC-treated rats as compared with untreated controls: sarcomas of the spleen and other organs; mesotheliomas of the abdominal cavity or scrotum in males; transitional-cell carcinomas of the urinary bladder in females; sc tissue fibromas in males; and mammary fibroadenomas and adenomas in females. In the mice, THC induced hemangiosarcomas at various sites in the males and hepatocellular carcinomas and adenomas in the females. The findings are consistent with those previously reported. It is concluded that under the conditions of this bioassay, THC is carcinogenic in male and female F344 rats and B6C3F1 mice. (30 refs)

79-6753 Bioassay of Butylated Hydroxytoluene (BHT) for Possible Carcinogenicity. (Eng) National Cancer In-

stitute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (150): 114 pp.; 1979.

Butylated hydroxytoluene (BHT) was tested for carcinogenicity by feeding to F344 rats and B6C3F1 mice. Two dose levels (3,000 and 6,000 ppm) were fed to rats (50 of each sex at each dose) for 105 wk and to mice for 107 or 108 wk. Matched controls of 20 untreated rats and 20 untreated mice of each sex were used. No significantly increased incidence of any tumors was found in treated rats compared with the corresponding controls. In female mice of the low-dose group, the incidence of carcinomas and adenomas of the bronchiolar or alveolar regions of the female low-dose mice was higher (16/46) than in the control group (1/20; $p < 0.01$). There was no significant increase in lung tumor incidence in the high-dose group of mice (7/50). Nonneoplastic lesions that occurred with greater frequency among the treated animals were focal alveolar histiocytosis in treated female rats and various liver lesions in treated male mice. Although BHT was not carcinogenic for the animals tested, its hepatotoxicity and possible lung tumorigenicity indicate that the compound should be retested. (33 refs)

79-6754 Bioassay of Cupferron for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (100): 65 pp.; 1978.

Cupferron (N-hydroxy-N-nitroso-benzenamine) was investigated for possible carcinogenicity by adding it to the feed of Fischer 344 rats and B6C3F1 mice. Groups of 49-50 males and 50 females of each species received one of two concentrations: the time-weighted av high and low dietary concentrations were, respectively, 0.30% and 0.15% for male and female rats and 0.4% and 0.2% for male and female mice. The 78-wk dosing period was followed by an observation period of up to 28 wk for the rats and up to 18 wk for the mice. Fifty males and 50 females of each species served as controls. Dosed rats had increased incidences of hepatocellular carcinomas, squamous cell carcinomas of the forestomach, hemangiosarcomas, gliomas, ganglioneuroma and tumors of the auditory sebaceous glands, which were all thought to be compound-related. Statistical analyses indicated that cupferron administration was associated with the increased incidence of hemangiosarcomas, squamous-cell carcinomas of the forestomach, and liver neoplasms in both sexes, and possibly was associated with the increased incidence of ganglioneuromas of the adrenal gland or adrenal medulla in males and of carcinomas of the Zymbal's gland in females. In mice, cupferron was associated with hemangiomas, hepatocellular carcinomas, and Zymbal's gland carcinomas in females and adenomas of the Harderian gland and hemangiosarcomas in both sexes. Statistical analysis indicated that cupferron administration was associated with the increased incidence of hemangiosarcomas in male mice and with the increased incidence of hepatocellular carcinomas, Harderian gland adenomas, hemangiosarcomas or hemangiomas, and possibly of carcinomas of the Zymbal's gland in female mice. A critique of the bioassay of cupferron for carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens is presented. (22 refs)

79-6755 Bioassay of p-Cresidine for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD

20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (142): 63 pp.; 1979.

p-Cresidine was tested for possible carcinogenicity in Fisher 344 rats and B6C3F1 mice given either of two time-weighted concentrations (0.5 and 1% for rats; 0.22, 0.22, 0.46 and 0.44 for low or high dose male or female mice, respectively) in the diet for ≤ 104 wk. Mortality rates were dose-related for both sexes in both species. A higher incidence of bladder carcinomas (papillary, squamous cell, transitional cell, and undifferentiated carcinomas) and of olfactory neuroblastomas in treated rats of both sexes and of hepato/cholangiocarcinomas in male rats was observed. A higher incidence of bladder carcinomas in mice of both sexes and of hepatocellular carcinomas in female mice was observed. It is concluded that, under the conditions of the assay, p-cresidine is carcinogenic to Fischer 344 rats and B6C3F1 mice of both sexes. (19 refs)

79-6756 Release of Repetitive Nuclear RNA into the Cytoplasm in Liver of Rats Fed 3'-Methyl-4-dimethylaminoazobenzene. (Eng) Patel, N. T. (Dept. Human Biological Chemistry, Univ. Texas Medical Branch, Galveston, TX 77550); Folse, D. S.; Holubek, V. *Cancer Res* 39(11): 4460-4465; 1979.

Metabolically active 3.5S RNA bound to nonhistone chromosomal proteins, one of the low-mol-wt nuclear RNA's present in rat liver, has nucleotide sequences copied from repetitive DNA and found in the chromatin of normal rat liver. In rats fed 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB, 100 ml/kg dry food) for 1, 3, or 10 wk, approx 17% of the nucleotide sequences of this RNA was released into the cytoplasm of the liver cells as parts of larger RNA molecules. With continuous 3'-MeDAB feeding, additional sequences of this nuclear RNA were released. After 16 wk of feeding, approx 35% of the nucleotide sequences were found in the cytoplasm. No such RNA release was observed in control animals fed noncarcinogenic aminoazobenzene. The process initiated by 3'-MeDAB which leads to the appearance in the cytoplasm of these nuclear RNA nucleotide sequences was irreversible and continued even when the feeding of the azocarcinogen was interrupted after 10 wk. Toxic effects of the 3'-MeDAB in the liver cells resulted in temporary changes in the cell population of the liver. The largest changes were observed after 10 wk of feeding, when many of the hepatocytes were larger than normal and the majority of the hepatocytes had enlarged nuclei and an altered chromatin appearance. With continuous feeding of 3'-MeDAB, the changes in liver morphology characteristic for animals fed 3'-MeDAB for 10 wk became less pronounced; and the liver morphology of animals fed 3'-MeDAB for 17 wk resembled that of control animals. The release of the nucleotide sequences does not appear to be related directly to the morphological changes in the liver observed during the early stages of the feeding of 3' MeDAB. (38 refs)

79-6757 Inhibition of 3'-Methyl-4-Dimethylaminoazobenzene (3' MeDAB)-induced Hepatocarcinogenesis in the Rat: Chloramphenicol Inhibits N,N-Dimethylaniline N-Oxidase and In Vitro Binding of [³H]3' MeDAB to Protein But Not to RNA. (Eng) Labuc, G. E. (Dept. Pathology, Univ. Melbourne, Parkville Victoria, 3052, Australia); Blunck, J. M. *Biochem Pharmacol* 28(19): 3032-3034; 1979.

The effects of chloramphenicol (CAP: 2% of the diet for 4 days) on the metabolic activation of 3'-methyl-4-dimethylaminoazobenzene (MDAB: 0.06% of the diet for 4 days) and the activity of N,N-dimethylaniline (DMA) N-oxidase were studied in male Sprague-Dawley rats. Liver microsomal DMA N-oxidase activity was reduced 17.5% by CAP ($P < 0.05$). MDAB had a similar effect, and combined feeding of CAP and MDAB produced a partially additive effect (26.2% inhibition). CAP (1 mM) also inhibited DMA N-oxidase activity 19.9% in vitro ($P < 0.05$). Similar trends were observed when microsomal 3'-methyl-4-dimethylaminoazobenzene reductase, 3'-methyl-4-dimethylaminoazobenzene N-demethylase, aminopyrine N-demethylase, and 3'-methyl-4-dimethylaminoazobenzene N-demethylase activities were observed in rats pair-fed MDAB and/or CAP. Binding of MDAB metabolites to PMS protein in vitro was decreased when rats were given CAP or CAP plus MDAB, but only if 3'-phosphoadenosine-5'-phosphosulfate was included in the incubation medium. There were no changes in the activation of MDAB to metabolites that bind to yeast RNA in vitro when MDAB and/or CAP were administered. (19 refs)

79-6758 Mutational Studies with Diquat and Paraquat In Vitro. (Eng) Benigni, R. (Istituto Superiore di Sanita, Rome, Italy); Bignami, M.; Carere, A.; Conti, G.; Conti, L.; Crebelli, R.; Dogliotti, E.; Gualandi, G.; Novelletto, A.; Ortali, V. A. *Mutat Res* 68(3): 183-193; 1979.

The mutagenicities of diquat and paraquat were tested in the following assay systems: Ames test in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat-liver microsomal fractions; resistance to 8-azaguanine in *S. typhimurium* strains hisG46, TA92, and TA1535; repair test in *S. typhimurium* strains TA1538 and TA1978; gene mutations in *Aspergillus nidulans*: 8-azaguanine (8-AG) resistance and methionine suppression (*meth* A1 locus); lethal recessive damage in *A. nidulans*; and unscheduled DNA synthesis (UDS) in human epithelial-like cells (EUE). Diquat and paraquat were positive in *S. typhimurium* (in the repair test and the 8-AG resistance system), in *A. nidulans* (for gene mutations and lethal recessive damage induction), and in EUE cells (UDS induction). (40 refs)

79-6759 Bioassay of 2-Chloro-p-Phenylenediamine Sulfate for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (113): 48 pp.; 1978.

The possible carcinogenicity of 2-chloro-p-phenylenediamine sulfate (CPS) was investigated in Fischer 344 rats and B6C3F1 mice. Groups of 50 males and 50 females of each species received one of two concentrations of CPS: in the chronic bioassay, the high and low doses for the rats were 0.3 and 0.15%, respectively, and for the mice they were 0.6 and 0.3%, respectively. The dosage period lasted for 105-107 wk in rats, 87 wk in high-dose mice, and 104-105 wk in low-dose mice. The high-dose mice were also observed for 18 wk after the dose period. Controls consisted of 20 males and 20 females of each sex. A variety of neoplasms were observed with approx equal frequency in the control and treated rats, as were a variety of degenerative, inflammatory, and proliferative lesions. With the exception of transitional-cell hyperplasia of the renal pelvis, none of the non-neoplastic lesions appeared to be related to CPS administration. It is concluded that

CPS is not carcinogenic in Fischer 344 rats. None of the statistical tests in male or female rats indicated a positive association between chemical administration and tumor incidence; however, the possibility of tumor induction in rats by CPS that could not be established under these test conditions is considered. In mice, dietary CPS administration was associated with an increased incidence of proliferative hepatocellular lesions compared with that in controls. However, no statistical evidence of the carcinogenicity of this compound was obtained for either male or female mice. (19 refs)

79-6760 Bioassay of Piperonyl Sulfoxide for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (124): 113 pp.; 1979.

The possible carcinogenicity of technical grade piperonyl sulfoxide (PS) was investigated in Fischer 344 rats and B6C3F1 mice. Groups of 50 male and 50 female rats received PS in their diet at either 1,500 or 3,000 ppm for males and either 3,000 or 6,000 ppm for females for 105 wk. Untreated rats of each sex (20) composed the control group. Groups of 50 male mice received either 350 or 700 ppm PS for 104 or 105 wk. Females initially received either 700 or 1,400 ppm, but the dose had to be reduced after wk 20 to 200 and 600 ppm, respectively, and the lower dosage period lasted for 84 or 85 wk. Matched controls consisted of 20 mice of each sex. The nature, incidence and severity of the lesions observed in dosed rats provided no clear evidence of a carcinogenic effect of PS. The incidence of hepatocellular carcinomas in male mice was associated with PS administration under the conditions of this assay; in females, the incidence of tumors could not be associated with PS administration. Thus, PS was not carcinogenic in male or female Fischer 344 rats or in female B6C3F1 mice, but was carcinogenic in male B6C3F1 mice. (23 refs)

79-6761 Triplet \leftarrow Singlet and Singlet \rightarrow Singlet Radiationless Transitions of Some Carcinogenic Compounds. (Eng) Abu-Zeid, M. E. (Physics Dept., Univ. Puerto Rico, Mayaguez, PR 00708); Perez, C.; Lopez, J. R.; Moreu, A.; Martinez, P.; Kollias, N. *J Photochemistry* 11(4): 219-226; 1979.

Radiationless transition rate parameters were determined for the following solutions: 3,4,9,10-dibenzopyrene-toluene, 20-methyl cholanthrene-benzene, 2-aminoanthracene-alcohol, and 1-aminoanthracene-alcohol. This was accomplished by measuring the fluorescence lifetimes of the compounds as a function of absolute temperature. Both monomer and excimer lifetimes were investigated. The temperature-independent part of the decay-time equation for these compounds was deemed the result of inter-system crossing or internal conversion for monomers and excimers. The temperature-dependent part was believed to be due to internal conversion, or to be of negligible value. (24 refs)

79-6762 Phthalic Anhydride. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (159): 1-107; 1979.

The carcinogenicity of phthalic anhydride was tested in 6-wk-old F344 rats and B6C3F1 mice. Male and female rats were fed the test

chemical at 7,500 or 15,000 ppm in the diet for 105 wk. Male mice received 25,000 or 50,000 ppm for 32 wk and 12,500 or 25,000 ppm for an additional 72 wk. Female mice received 25,000 or 50,000 ppm for 32 wk and then 6,250 or 12,500 ppm for 72 wk. On the basis of histological findings, there appeared to be no difference between the experimental and control rat groups with regard to frequency or distribution of neoplasms, except for malignant lymphoma in the female rats (1/20, 11/50, and 4/50 for control, low-, and high-dose females). However, due to the high and fluctuating incidence of malignant lymphoma in control F344 rats, these differences were not considered to be related to administration of the compound. In female rats, the incidence of alveolar/bronchiolar adenomas was significantly increased according to the Cochran-Armitage test ($p = 0.020$) but not to the Fischer exact test. According to both histological examination and statistical analyses, there was no increased incidence of tumors at any site in experimental male or female mice. It is concluded that phthalic anhydride is not carcinogenic in F344 rats or B6C3F1 mice of either sex. (9 refs)

79-6763 p-Quinone Dioxime. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (179): 1-50; 1979.

The carcinogenicity of p-quinone dioxime (dioxime 2,5-cyclohexadiene-1,4-dione) was tested in 6-wk-old Fischer 344 rats and B6C3F1 mice. The animals were fed the test compound in the diet for 104 wk at two dose levels: 375 ppm and 750 ppm for the rats and 750 ppm and 1,500 ppm for the mice. In rats given p-quinone dioxime, there was an increased incidence of neoplasms of the urinary tract, with bladder neoplasms occurring predominantly in females (0/16, 0/45, and 2/46 in control, low-, and high-dose males, respectively, and 0/19, 3/43, and 11/44 in control, low-, and high-dose females) and kidney tumors occurring only in males (0/20, 1/49, and 3/50 in control, low-, and high-dose groups, respectively). Statistical tests indicated a significant positive association between p-quinone dioxime administration and urinary tract tumors in female rats but not in male rats. Vascular neoplasms of the spleen were observed only in experimental mice, but the data did not give conclusive evidence of carcinogenicity at the doses administered. In female mice, there was a positive association between p-quinone dioxime administration and the incidence of hepatocellular neoplasms according to the Cochran-Armitage statistical test ($p = 0.027$) but not according to Fischer exact tests. It is concluded that dietary administration of p-quinone dioxime is carcinogenic in female Fischer 344 rats but not in male rats or B6C3F1 mice of either sex. (16 refs)

79-6764 Bioassay of Diazinon for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (137): 96 pp.; 1979.

The possible carcinogenicity of diazinon was assessed in F344 rats and B6C3F1 mice. Groups of 50 rats or mice of either sex were fed a diet containing one of two concentrations of the test chemical (400 or 800 ppm for the rats, 100 or 200 ppm for the mice) for 103 wk. Groups of 25 matched animals fed a normal diet were used as controls. Treatment had no effect on mean body wt, mortality, or tumor incidence. Some hyperactivity was observed in treated animals of both species and both sexes. It is concluded that, under the conditions of the assay, diazinon is not carcinogenic in F344 rats or B6C3F1 mice. (21 refs)

79-6765 Bioassay of Parathion for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (70): 104 pp.; 1979.

The carcinogenicity of technical grade parathion (32 or 63 ppm for male rats and 23 or 45 ppm for female rats, in the feed for 32-33 wk; and 80 or 160 ppm for mice, in the feed for 62-80 wk) was studied in Osborne-Mendel rats and B6C3F1 mice. Body wts of the male mice and high-dose male and female rats were lower than those of controls throughout the study. In the rats, there were dose-related increases in the incidence of cortical adenomas or carcinomas of the adrenal cortex. Although the incidences did not differ significantly from those in corresponding matched controls, they were higher than those in corresponding historical controls from the same laboratory. There were no significant increases in tumor incidence in the male or female mice. It was concluded that under the conditions of this bioassay, parathion is not carcinogenic for B6C3F1 mice but that it is probably carcinogenic for Osborne-Mendel rats. (19 refs)

79-6766 Bioassay of Azobenzene for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (154): 112 pp.; 1979.

Azobenzene was tested for possible carcinogenicity in F344 rats and B6C3F1 mice. Groups of 50 rats of each sex received a diet containing the test chemical at 200 or 400 ppm for 105 or 106 wk; controls consisted of 20 untreated, matched animals of each sex. Groups of 50 female mice received a diet containing the test chemical at 400 or 800 ppm for 38 wk, and, because of excessive wasting, 100 and 400 ppm for the subsequent 67 or 68 wk. Controls consisted of 20 untreated, matched mice of each sex. Mean body wt was lower in treated than in control animals and was generally dose-related. Mortality was dose-related in male rats and female mice but was not affected by treatment in female rats and male mice. Large numbers of sarcomas (fibrosarcomas, hemangiosarcomas, osteosarcomas) of the spleen and other abdominal organs were observed in rats of both sexes, and hemangiopericytomas occurred frequently in female rats; their incidence was dose-related. The incidence of tumors in mice of both sexes was not affected by treatment. It is concluded that, under the conditions of the assay, azobenzene is carcinogenic (sarcomagenic) for F344 rats but not for B6C3F1 mice. (21 refs)

79-6767 N-Glucuronidation of N-Hydroxy Aromatic Amines: A Mechanism for Their Transport and Bladder-specific Carcinogenicity. (Eng) Poupko, J. M. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL 33101); Hearn, W. L.; Radomski, J. L. *Toxicol Appl Pharmacol* 50(3): 479-484; 1979.

Glucuronide conjugates of carcinogenic N-hydroxy metabolites of the primary aromatic amines 4-aminobiphenyl (4-ABP), 2-naphthylamine (2-NA), and 1-naphthylamine (1-NA) were isolated from the urine of dogs given one of the drugs (10 mg/kg, 55 mg/kg, or 95 mg/kg po, respectively) and from the in vitro incubation of N-hydroxy metabolites with uridine-5'-diphosphoglucuronic acid-fortified dog liver microsomes. The urinary and microsomal conjugates were purified by several sequential chromatographic procedures, including Sephadex G-15, Amberlite

XAD-2, and cellulose CF-11 chromatography for microsomal conjugates and Sephadex G-10, DEAE, and Amberlite XAD-2 chromatography for urinary conjugates. The infrared spectra of purified urinary and microsomal conjugates of these three N-hydroxy aromatic amines were identical to spectra of authentic N-C glucuronides prepared by two different synthetic procedures. The urinary and microsomal conjugates comigrated with synthetic N-C glucuronides in two solvent systems. In conjunction with previous studies, these observations provide evidence that N-C glucuronidation represents the general metabolic reaction of carcinogenic N-hydroxy aromatic amines that leads to transport of these compounds to their site of action in the bladder. (18 refs)

- 79-6768 Assay for Mutagenicity of Bile in Sprague-Dawley Rats Treated Subcutaneously with Intestinal Carcinogens. (Eng) Moriya, M. (Toxicology Div., Inst. Environmental Toxicology, Suzuki-cho 2-772, Kodaira-shi, Tokyo 187, Japan); Ohta, T.; Sugiyama, F.; Miyazawa, T.; Shirasu, Y. *J Natl Cancer Inst* 63(4): 977-982; 1979.

The mode of action of sc-injected intestinal carcinogens was investigated by testing the mutagenicity of bile collected from noninbred Sprague-Dawley rats treated sc with these carcinogens in the presence and absence of β -glucuronidase. Bile samples from rats inoculated with 4-aminobiphenyl were mutagenic for *Salmonella typhimurium* TA100 only in the presence of β -glucuronidase, whereas those from 3,2'-dimethyl-4-aminobiphenyl-treated rats did not require the enzyme for mutagenicity in strain TA100. Bile from rats inoculated with 1,2-dimethylhydrazine, azoxymethane, or methylazoxymethanol acetate was not mutagenic in *S. typhimurium* strains G46 and TA100, whether β -glucuronidase was added or not; however, these carcinogens were highly mutagenic for strain G46 in the *Salmonella*-microsome mutagenicity test and/or in the host-mediated assay. (33 refs)

- 79-6769 Bioassay of 3,3'-Dimethoxybenzidine-4,4'-Diisocyanate for Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (128): 60 pp.; 1979.

A bioassay for the possible carcinogenicity of 3,3'-dimethoxybenzidine-4,4'-diisocyanate was conducted by administering the test chemical to groups of male or female F344 rats or B6C3F1 mice for 78 consecutive wk. In the rat bioassay, the test chemical was administered by gavage for the first 22 wk (3,000 or 1,500 mg/kg) and in the feed thereafter. The high and low concentrations used in the feed of both mice and rats were 44,000 and 22,000 ppm, respectively. A positive correlation between treatment and mortality was observed. Significantly increased incidences of leukemia and lymphoma in treated rats of both sexes, of skin neoplasms in treated male rats, and endometrial stromal polyps in female rats were observed. Treatment was also associated with the development of a combination of squamous cell carcinoma and sebaceous carcinoma of the Zymbal's gland and skin of the ear in rats of both sexes. It is concluded that 3,3'-dimethoxybenzidine-4,4'-diisocyanate is carcinogenic in F344 rats of both sexes, under the conditions of the assay. (18 refs)

- 79-6770 Panmyelopathy and Metastasizing Hemangioendothelioma of the Liver After Thorotrast Use. Late

Effects of Thorotrast Use in Man. (Ger) Thiel, H. (Medizinische Universitätsklinik und Poliklinik, Krankenhaus Bergmannsheil Bochum, Hunscheidtstrasse 1, D-4630 Bochum 1, W. Germany); Schott, D.; Schejbal, V.; Horster, H. G. *Med Klin* 74(40): 1451-1455; 1979.

Two patients in whom late effects of thorotrast (thorium dioxide) were diagnosed are described. A hemangioendothelioma of the liver and metastases in the lungs and thyroid were found during autopsy of a 61-yr-old man who had undergone thorotrast femoral angiography 36 yr previously. Thorotrast deposits in his liver, spleen, and abdominal lymph nodes were found during screening for thorotrast damage 7 yr before his final illness. The results of whole-body counting suggested that the thorotrast dose was approx 80 ml. At autopsy, thorotrast deposits were found, next to the liver tumor, in the portal circulation, and especially in the fibrous, calcified, 40-g spleen. An aplastic blood syndrome was diagnosed in a 56-yr-old patient who had been given thorotrast (estimated dose, 17 ml) 34 yr previously for carotid angiography. Thorotrast deposits were found in the liver, spleen, and bone marrow. Thorotrast was used in diagnosis until 1956. Regular follow-up at 1- to 2-yr intervals of persons previously given thorotrast is recommended. (31 refs)

- 79-6771 Histopathological Changes Induced in the Urinary Bladder and Liver of Female BALB/c Mice Treated Simultaneously with 2-Naphthylamine and Cyclophosphamide. (Eng) Yoshida, M. (Second Dept. Pathology, Sch. Medicine, Tokushima Univ., Kuramoto-cho 3-chome, Tokushima 770, Japan); Numoto, S.; Otsuka, H. *Gann* 70(5): 645-652; 1979.

The effect of 2-naphthylamine and cyclophosphamide on the urinary bladder and liver of female BALB/c mice was investigated. The bladder mucosa of mice treated with 2-naphthylamine alone (2,000 ppm in the diet) for 40 wk showed diffuse hyperplasia. Administration of 2-naphthylamine for 40 wk plus injections of cyclophosphamide (200 mg/kg body wt) produced bladder carcinomas, associated with downward growth of the bladder epithelium in approx 30.8-35.7% of the animals. All the bladder carcinomas were of the transitional cell type and most of them contained pseudoglandular areas. There was a higher incidence of hepatomas in mice treated with 2-naphthylamine plus cyclophosphamide than in mice treated with 2-naphthylamine alone. Most of the hepatomas were solitary and showed a trabecular pattern. Cyclophosphamide seemed to have a promoting effect on carcinogenesis of the bladder mucosa and liver induced by 2-naphthylamine in female BALB/c mice. (19 refs)

- 79-6772 Bioassay of 1,5-Naphthalenediamine for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (143): 59 pp.; 1978.

A bioassay of 1,5-naphthalenediamine for possible carcinogenicity was conducted by feeding groups of 50 F344 rats or B6C3F1 mice of each sex a diet containing the test chemical at either of two concentrations (0.1% and 0.05% for rats; 0.2% and 0.1% for mice) for 103 wk. Groups of 50 mice and 25 rats of each sex fed a normal diet were used as controls. No correlation between treatment and mortality was observed. A significantly increased incidence of endometrial stromal polyps (sometimes undergoing transformation to endometrial stromal sarcomas) and of either adenomas or carcinomas of the clitoral gland was observed in female rats. An in-

CHEMICAL CARCINOGENESIS

creased incidence of thyroid neoplasms was observed in mice of both sexes (papillary carcinomas, follicular-cell adenomas, and papillary cystadenomas in both sexes; C-cell carcinomas in females). A significant increase of hepatocellular carcinomas and alveolar/bronchial adenomas was observed in female mice. It is concluded that, under the conditions of the assay, 1,5-naphthalenediamine is carcinogenic in female F344 rats and B6C3F1 mice of both sexes. (8 refs)

79-6773 Long-Term Toxicologic Studies of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Laboratory Animals. (Eng) Kociba, R. J. (Toxicology Res. Lab., Health and Environmental Res., Dow Chemical Co., Midland, MI 48640). Keyes, D. G.; Beyer, J. E.; Carreon, R. M.; Gehring, P. J. *Ann NY Acad Sci* 320:397-404; 1979.

The chronic toxicity and carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD: 0.001-0.1 µg/kg/day in the diet for 2 yr) were studied in male and female Sprague-Dawley rats. The highest dose level caused multiple toxicologic effects. Liver toxicity was consistently observed, and this was accompanied by morphologic changes in the lymphoid, respiratory, and vascular tissues. There was an increased incidence of hepatocellular carcinoma and squamous cell carcinoma of the lung, hard palate/nasal turbinates, and tongue at this dose level. However, the incidences of pituitary, uterine, mammary gland, pancreatic, and adrenal medullary tumors were decreased at this dose level. The incidences of other spontaneous lesions such as chronic renal disease were also decreased. A lesser degree of toxicity, primarily of the liver, was seen in animals given 0.01 µg/kg/day TCDD, but the incidence of neoplasms was not increased at this dose level. No adverse effects were seen in rats given 0.001 µg/kg/day TCDD, although the liver and fat contained 540 ppt TCDD at the termination of the study. (8 refs)

79-6774 2,7-Dichlorodibenzo-*p*-dioxin. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (123): 1-103; 1979.

The carcinogenicity of 2,7-dichlorodibenzo-*p*-dioxin (DCDD) which is found as a by-product in the manufacture of pentachlorophenol and in the herbicide 2,4,5-trichlorophenoxyacetic acid and its esters, was studied in B6C3F1 mice and Osborne-Mendel rats. DCDD was incorporated in the diet at 5,000 or 10,000 ppm for 110 wk. Survival was not decreased in DCDD-treated animals, and tumor incidence was not significantly increased in DCDD-treated rats or female mice. Although the incidence of hepatocellular tumors increased with increasing dose in male mice, the significance of this finding was questioned based on past experience in this laboratory. There were significant increases in the incidences of leukemias or lymphomas ($p = 0.006$) and hemangiomas or hemangiosarcomas ($p = 0.028$) in male mice given the high DCDD dose compared with low-dose and control groups, but the incidences of these tumors showed no increase with increasing dose, and the findings were of questionable significance. It is concluded that under the conditions of this bioassay, DCDD is not carcinogenic in Osborne-Mendel rats or female B6C3F1 mice but that it may be carcinogenic in male B6C3F1 mice. (20 refs)

79-6775 Dibutyltin Diacetate. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (183): 45 pp.; 1979.

The carcinogenicity of dibutyltin diacetate (DBDA: 62.5-250 ppm in the diet for 26 wk) for Fischer 344 rats and B6C3F1 mice was studied. Subchronic toxicity tests with DBDA were also conducted in the same strains. Mortality increased in a dose-dependent fashion in DBDA-treated male rats and female mice, and mean body wt was decreased in male mice. Tumor incidence was not significantly increased in DBDA-treated rats or male mice relative to untreated controls. However, there was an increase in uterine neoplasms among DBDA-treated female rats and this, coupled with the fact that many tissues from the female rats were lost prior to microscopic examination, was taken as an indication that DBDA may be carcinogenic in these animals. The incidence of hepatocellular adenomas increased with DBDA dose in the female mice, but these data were not significant. Thus, there is no conclusive evidence that DBDA is carcinogenic in male Fischer 344 rats or male or female B6C3F1 mice. (15 refs)

79-6776 Mutagenicity of Pyrrolizidine Alkaloids in the Salmonella/Mammalian-Microsome Test. (Eng) Yamanaka, H. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan); Nagao, M.; Sugimura, T.; Furuya, T.; Shirai, A.; Matsushima, T. *Mutat Res* 68(3): 211-216; 1979.

The mutagenicities of B pyrrolizidine alkaloids were studied. Clivorine, fukinotoxin, nelioetrine, lasiocarpine, ligularidine, LX201, and senkirkine, were mutagenic in the Ames's test (*Salmonella typhimurium* strain TA100). Preincubation of these alkaloids with S9 mix and bacteria in a liquid medium was essential for the demonstration of their mutagenicities. (24 refs)

79-6777 Bioassay of Azinphosmethyl for Possible Carcinogenicity. (Eng) National Cancer Institute (Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (69): 126 pp.; 1979.

The carcinogenicity of technical grade azinphosmethyl (APM, 78 or 156 ppm for male rats, 62.5 or 125 ppm for female rats, 31.3 or 62.5 ppm for male mice, and 62.5 or 125 ppm for female mice, incorporated in the feed for 80 wk) for Osborne-Mendel rats and B6C3F1 mice was studied. Body wts of male rats and mice and high-dose female rats and mice were lower than those of controls throughout the study, and typical signs of organophosphate poisoning were observed in some animals. Many tumors of the endocrine organs were observed in the rats, but the incidences in most cases were not significantly higher than in the matched controls. However, the incidence of tumors of the pancreatic islets and the follicular cells of the thyroid in the male rats suggested that APM is a carcinogen in these animals. There was no increase in tumor incidence in the mice that could be attributed to APM feeding. Thus, under the conditions of this bioassay, APM was not carcinogenic for male or female B6C3F1 mice or female Osborne-Mendel rats. (18 refs)

79-6778 3-Sulfolene. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (102): 1-46; 1979.

The carcinogenicity of 3-sulfolene (an intermediate in the production of petroleum, plastics, and textiles) was studied in Osborne-

Mendel rats and B6C3F1 mice. 3-Sulfolene (200-560 mg/kg for rats and 100-300 mg/kg for mice) was given by gavage 5 days/wk over 15 4-wk periods, each treatment period being preceded by a week in which no drug was given. Subchronic toxicity tests were conducted to determine max tolerated dosages. Although 3-sulfolene caused dose-dependent increases in mortality rate among both rats and mice, most animals lived long enough to be at risk for late-developing tumors. Accelerated mortality was associated with toxicity to the circulatory, urinary, biliary, and reproductive systems. There were dose-dependent increases in the incidence of hepatocellular carcinoma in 3-sulfolene-treated male mice compared with untreated controls, but the increases were not statistically significant. There were no other positive associations between 3-sulfolene treatment and tumor incidence. It is concluded that under the conditions of this bioassay, 3-sulfolene is not carcinogenic for Osborne-Mendel rats or for B6C3F1 mice. (15 refs)

- 79-6779 Induction of Hepatic Neoplastic Lesions in Mice With a Single Dose of Hycanthone Methanesulfonate After Partial Hepatectomy. (Eng) Tsuda, H. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Sarma, D. S.; Rajalakshmi, S.; Zubroff, J.; Farber, E.; Batzinger, R. P.; Cha, Y. N.; Bueding, E. *Cancer Res* 39(11): 4491-4496; 1979.

Experiments were designed to determine whether hycanthone methanesulfonate [1-((2-(diethylamino)ethyl) amino)-4-(hydroxymethyl)thioxanthene-9-one monomethanesulfonate], an antischistosomal drug, and its analog, IA-4-N-oxide [8-chloro-2-(2-(diethylamino)ethyl)-2H-[1]benzothioapyrano[4,3,2-cd]indazole 5-methanol monomethanesulfonate], will induce neoplastic lesions in the liver of mice not infected with *Schistosoma mansoni*. All the mice received a single im injection of hycanthone methanesulfonate (76 mg/kg), IA-4-N-oxide (80 mg/kg), or an equivalent dose of the solvent, 0.9% NaCl soln, 42 hr after partial hepatectomy. Of the mice receiving hycanthone methanesulfonate and living 200 days or longer, 11.5% had hepatocellular carcinoma and 4.2% had liver sarcoma. These malignant neoplasms were not seen in the animals receiving either IA-4-N-oxide or 0.9% NaCl solution. In addition, mice receiving hycanthone methanesulfonate showed a significantly higher incidence of both type 1 (43% compared to 21% in controls) and type 2 (21% compared to 12% in controls) hepatocyte neoplasms. Mice receiving IA-4-oxide showed no increased incidence of neoplasms. (30 refs)

- 79-6780 Bioassay of Aldicarb for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (136): 106 pp.; 1979.

A bioassay of aldicarb for possible carcinogenicity was conducted in F344 rats and B6C3F1 mice. Groups of 50 rats or mice of each sex received the test chemical in feed at either 2 or 6 ppm for 103 wk. Groups of 25 animals were used as matched controls. No significant difference in mean body wt between treated or control animals was observed, and treatment did not affect survival. Hyperactivity was observed in treated mice. No correlation between treatment and the incidence of tumors was observed. It is concluded that, under the conditions of the test, aldicarb is not carcinogenic in F344 rats or B6C3F1 mice of either sex. (29 refs)

- 79-6781 Investigation into the Mutagenic Activity of Azathioprine (Imuran) in Different Test Systems.

(Eng) van Went, G. F. (Lab. Pharmacology, Natl. Inst. Public Health, P.O. Box 1, 3720 BA Bilthoven, Netherlands). *Mutat Res* 68(2): 153-162; 1979.

Chromosome damage induced by azathioprine (Imuran) was investigated in the micronucleus test with mice and rats, in the pertussis-stimulated lymphocyte metaphase test with rabbits, and in children on azathioprine therapy. In the micronucleus test, there was a dose-dependent increase in the number of cells with micronuclei. Doses given ip twice in 24 hr were 25, 50 and 100 mg/kg body wt for mice and 50, 100 and 200 mg/kg for rats. In the lymphocyte test, a dose of either 5 or 20 mg/kg body wt was given po to rabbits on three successive days after pertussis injection. These treatments induced a significantly increased number of cells with chromosomal abnormalities as compared with controls. These results were confirmed by observations of increased numbers of structural chromosome abnormalities in lymphocyte cultures of children on long-term azathioprine therapy. (42 refs)

- 79-6782 Carcinomas of the Liver in Rats Ingesting Kepone. (Eng) Reuber, M. D. (Frederick Cancer Res. Center, Frederick, MD 21701). *Neoplasma* 26(2): 231-235; 1979.

Young male and female albino rats ingested 0, 1, 5, 10 or 25 ppm decachloroocta-hydro-1,3,4-methano-2H-cyclobuta(d) pentalen-2-one (Kepone), an organochlorine pesticide, in the diet for 2 yr. Carcinomas of the liver, as well as hyperplastic nodules and moderate and severe diffuse hyperplasia, were observed in Kepone-treated rats, but not in controls. Female rats ingesting Kepone were more susceptible than male rats to hepatic carcinogenesis. Rats ingesting 50 or 80 ppm Kepone developed severe diffuse hepatic hyperplasia and did not survive beyond 26 wk. (28 refs)

- 79-6783 Cytogenetic Effect of Methotrexate on Human Cells In Vivo. Comparison Between Results Obtained by Chromosome Studies on Bone-Marrow Cells and Blood Lymphocytes and by the Micronucleus Test. (Eng) Jensen, M. K. (Section Hematology, Dept. Medicine B, Aalborg Hosp., 9100 Aalborg, Denmark); Nyfors, A. *Mutat Res* 64(5): 339-343; 1979.

The mutagenic effect of methotrexate (MTX: 25-50 mg, im or po) on the cells of 22 patients was studied via chromosome studies on bone-marrow cells and blood lymphocytes and via the micronucleus test. Examination of bone-marrow aspirates from 18 MTX-treated patients demonstrated structural aberrations in 0%-10% of metaphases (mean, 4.0%), compared with 0%-4% of metaphases (mean, 1.4%) in 10 control bone marrow preparations ($p < 0.005$). The aberrations were mainly breaks of the chromatid and chromosomal types. Structural aberrations (chromatid breaks) were observed in 0%-2% of metaphases (mean, 0.5%) in the lymphocyte cultures of seven MTX-treated patients studied, compared with 2% of the metaphases of control cultures. Micronuclei were present in 0%-32% of the erythroblasts from 10 MTX-treated patients (mean, 12.0%), compared with 0%-4% (mean 0.68%) of the erythroblasts from control subjects ($p < 0.0005$). No erythroblasts with micronuclei were seen in three patients with psoriasis who had not received MTX. The data indicate that future studies of the possible cytogenetic effects of chemical agents must include examinations of bone marrow cells and suggest that the micronucleus test may be more sensitive in detecting mutagenic effects than chromosome studies. (17 refs)

- 79-6784 Mutagenic and Colicine-inducing Activity of Two Antioxidants: Pyrogallol and Purpurogallin. (Eng) Ben-Gurion, R. (Israel Inst. Biological Res., Ness-Ziona, Israel). *Mutat Res* 68(3): 201-205; 1979.

The antioxidant pyrogallol (PYL) and its oxidative derivative purpurogallin (PUL) were tested for ability to induce colicine and for mutagenicity in the Ames test. Both substances induced colicine E2 when tested directly on test plates; the most effective dose for PYL was 200 µg/plate and for PUL, was 100 µg/plate in the presence of a liver microsomal preparation. The mutagenicity of PUL and PYL was tested with the TA1537 and TA100 strains of *Salmonella typhimurium*. PYL was mutagenic in these strains at doses of 20-200 µg/plate; its mutagenicity was reduced in the presence of a rat liver microsomal preparation. PUL was only weakly mutagenic in these two strains, even at doses (300-600 µg/plate) much higher than those needed to induce colicine. In an attempt to overcome the problem produced by the long exposure to PUL on the test plates, the bacteria were exposed to PUL in nutrient broth for shorter periods of time and diluted on test plates; viable bacteria were counted, and the number of mutants/survivor was calculated. The results revealed that PUL was highly mutagenic for exposure times of up to 4 hr. When the mutants grown on the PUL plates were mixed with the original tester strain and the growing mixture tested for sensitivity towards the killing effects of PUL, it was found that the mutants in the mixture were as sensitive to cell killing as the parent strain. It was concluded that PYL and the food additive PUL represent potential health hazards with regard to mutagenesis and carcinogenesis. (7 refs)

- 79-6785 Mutagenicity Tests with Griseofulvin. (Eng) Leonard, A. (Mammalian Genetics Lab., Dept. Radiobiology, C.E.N.-S.C.K., B 2400 Mol, Belgium); Poncelet, F.; Grutman, G.; Carbonelle, E.; Fabry, L. *Mutat Res* 68(3): 225-234; 1979.

The clastogenic properties of griseofulvin were studied in male BALB/c mice given the drug ip (0.5-2.0 g/kg); the genetic effects in *Salmonella typhimurium* were also investigated. In mice, bone marrow cells were examined for micronucleated RBC and chromosomal aberrations, and pre- and postmeiotic cells were examined for reciprocal translocations or dominant lethal mutations, respectively. In *S. typhimurium*, the induction of his⁺ revertants was studied. All tests for mutagenicity were negative with griseofulvin, whereas highly significant effects were obtained in positive control assays with thio-TEPA [tris(1-aziridinyl)phosphine sulfide; 1.25-20 mg/kg, ip]. (35 refs)

- 79-6786 Inhibition of DNA Synthesis in Cultured Lymphocytes and Tumor Cells by Extracts of Betel Nut, Tobacco, and Miang Leaf, Plant Substances Associated with Cancer of the Ororespiratory Epithelium. (Eng) Yang, J. A. (Dept. Surgery, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Huber, S. A.; Lucas, Z. J. *Cancer Res* 39(12): 4802-4809; 1979.

The high incidence of oropharyngeal, esophageal, and laryngeal cancers in certain parts of the world has been attributed to conjugated tannins found in certain folk medicinal herbs. Miang leaf and betel nut extracts prepared with phosphate-buffered saline inhibited [³H]thymidine incorporation by phytohemagglutinin-stimulated human lymphocytes and by rat mammary tumor and mouse L-cells in logarithmic growth. Pretreating the lymphocytes for 1 or 4 hr with the extracts inhibited phytohemagglutinin-

induced thymidine incorporation 72 hr later. At concentrations of 2.5 volumes % or lower, miang and betel nut extracts inhibited thymidine incorporation 40%-98% without any apparent signs of toxicity as demonstrated by the ⁸⁶Rb equilibrium assay. Neither extract inhibited cytotoxicity of rat mammary tumor cells by immune syngeneic spleen cells. The inhibitory factors had mol wts between 1,000 and 10,000 daltons as determined by ultrafiltration and were unaffected by boiling for 3 min or by treatment with alcohol; therefore they are probably not proteins. This in vitro demonstration of inhibition of DNA synthesis by these plant extracts presumably enriched for conjugated tannins may relate to inhibition of growth of rats and chickens fed conjugated tannin-contaminated sorghum feed. The carcinogenic potential of either these extracts or conjugated tannins is not yet established. (33 refs)

- 79-6787 Inhibition of Aflatoxin-induced Serum α -Fetoprotein in Rats Fed Cauliflower. (Eng) Boyd, J. N. (Dept. Food Science and Technology, Inst. Food Science, New York State Agricultural Experiment Station, Cornell Univ., Geneva, NY 14456); Sell, S.; Stoewsand, G. S. *Proc Soc Exp Biol Med* 161(4): 473-475; 1979.

The effect of aflatoxin B₁ (AB: 1 ppm in diet for 5 wk) and cauliflower (added to the diet for 5 wk) on serum α -fetoprotein (AFP) levels was studied in male Fischer 344 Sch, rats. Serum AFP levels were similar in rats fed control and cauliflower-containing diets. AB significantly increased serum AFP levels, which had been reduced by cauliflower consumption; AFP levels in animals fed AB plus cauliflower were similar to those in rats fed the control diets. Cauliflower enhanced hepatic aminopyrine N-demethylase activity, and this activity was not altered by AB treatment. Hepatic mixed function oxidase activity was not significantly altered by AB feeding. The results suggest that the reduced serum AFP levels in rats given AB plus cauliflower are indicative of the ability of dietary cauliflower to protect against AB-induced hepatocarcinoma. (22 refs)

- 79-6788 In Vitro Effects of Aflatoxin B₁ on the Uptake of ¹⁴C-orotic Acid Into Kidney, Liver and Muscle Tissue of the Mongolian Gerbil, *Meriones unguiculatus*. (Eng) Kinzie, J. M. (Dept. Biology, Virginia Commonwealth Univ., Richmond, VA 23284); Llewellyn, G. C. *Bull Environ Contam Toxicol* 23(4/5): 491-496; 1979.

The effects of aflatoxin B₁ (AFB) on the uptake of ¹⁴C-orotic acid (OA) into kidney, liver, and muscle tissue of the Mongolian gerbil (*Meriones unguiculatus*) in vitro were studied. In tissues treated with 1.25 µg/ml AFB, there was no clear effect on OA uptake by kidney or muscle, although hepatic uptake appeared to be depressed, especially in the male. At 2.50 µg/ml, OA uptake was clearly depressed in all tissues from female gerbils, but the results were ambiguous and insignificant in male tissues. The overall sensitivity of the tissues to AFB appeared to be: liver > muscle > kidney. (13 refs)

- 79-6789 Production and Characterization of Antibody Against Aflatoxin M₁. (Eng) Harder, W. O. (Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI 53706); Chu, F. S. *Experientia* 35(8): 1104-1107; 1979.

Antibody against aflatoxin M₁ was obtained after immunization of rabbits with bovine serum albumin-aflatoxin M₁ oxime conjugate. The antibody had greatest binding efficiency for aflatoxin M₁ and was less efficient for aflatoxin B₁. Cross-reaction of antibody with aflatoxin Q₁, aflatoxicol, and aflatoxin B₂ was weak. Aflatoxin B₂, aflatoxin G₁, aflatoxin G₂, and aflatoxin B₁-guanine adduct showed almost no cross-reaction with the antibody. The sensitivity of the binding assay for aflatoxin M₁ detection was in the range of 1-10 ng per assay. Detailed methods for the preparation of the conjugate, production of immune serum, and methods for antibody determination are described. (24 refs)

- 79-6790 Induction of Osteogenic Sarcomas and Tumors of the Hepatobiliary System in Nonhuman Primates with Aflatoxin B₁. (Eng) Sieber, S. M. (Lab. Chemical Pharmacology, NCI, Bethesda, MD 20205); Correa, P.; Dalgard, D. W.; Adamson, R. H. *Cancer Res* 39(11): 4545-4554; 1979.

Ongoing studies on the carcinogenicity of aflatoxin B₁ (AFB₁) in nonhuman primates are updated. A total of 47 Old World monkeys, chiefly rhesus and cynomolgus, received AFB₁ ip (0.125-0.25 mg/kg) and/or po (0.1-0.8 mg/kg) for 2 mo or longer, and 12 are currently alive and without evidence of tumor. Of the 35 monkeys necropsied to date, 13 (37%) developed one or more malignant neoplasms, yielding an overall tumor incidence of 28%. Five of the neoplasms were primary liver tumors (2 hepatocellular carcinomas and 3 hemangioendothelial sarcomas), and 2 cases of osteogenic sarcoma were found. Other tumors diagnosed were 6 carcinomas of the gallbladder or bile duct, 3 tumors of the pancreas or its ducts, and one papillary Grade 1 carcinoma of the urinary bladder. The tumors developed in animals receiving an average total AFB₁ dose of 709 mg (range, 99-1,354 mg) for an average of 114 mo (range, 47-147 mo). Of the 22 necropsied monkeys without tumor, 15 (68%) showed histological evidence of liver damage, including toxic hepatitis, cirrhosis, and hyperplastic liver nodules. These animals had received an average total AFB₁ dose of 363 mg (range, 0.35-1,368 mg) for an average of 55 mo (range, 2-141 mo). The results indicate that AFB₁ is a potent hepatotoxin and carcinogen in nonhuman primates and further support the hypothesis that humans exposed to this substance may be at risk of developing cancer. (33 refs)

- 79-6791 The Effect of Amaranth on the Rapid Onset of Liver Cancer Induced by Aflatoxin B₁. (Eng) Nizami, H. M. (Pakistan Medical Res. Council, Res. Center JPMC, Karachi, Pakistan); Nizami, F.; Zuberi, S. J. *Lav Ist Anat Istol Patol Perugia* 38(3): 87-90; 1978.

The cocarcinogenic activity of amaranth dye (15 mg/wk for 10 wk, by gastric intubation), which has anti-vitamin A activity in the liver, on the early onset of liver cancer induced by aflatoxin B₁ (AFB₁: 15 mg/kg for 10 wk, by gastric intubation) was studied in male JPMC rats. Weight gain was depressed in rats that received amaranth alone, compared with that in untreated controls. Weight loss was also observed in rats given amaranth plus AFB₁, and liver tumors and hemorrhagic areas were found. Death in these animals occurred during the 9th and 11th wk of treatment. Similar liver tumors were found in animals given AFB₁ only, but these mice did not die until the 15th wk. The wet weights of the livers of animals given AFB₁ plus amaranth were less than those of the livers of animals given AFB₁ alone. Agents like amaranth lower body resistance and may act as cocarcinogens in promoting earlier carcinogenesis and mortality. (5 refs)

- 79-6792 1-Amino-2-methylantraquinone. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (111): 1-68; 1979.

The carcinogenicity of 1-amino-2-methylantraquinone (AMAQ), an intermediate in the synthesis of anthraquinone dyes and a dye itself, in Fischer 344 rats and B6C3F₁ mice was studied. AMAQ was added to the rats' diet at 0.06% or 0.03% for 17 wk and 0.24% or 0.12% for an additional 62 wk. In mice, the dose was 0.06% for 78 wk or 0.03% for 16 wk, 0.12% for an additional 26 wk, and 0.03% for 31 wk thereafter. Subchronic feeding studies were also conducted. In the chronic study, the incidences of hepatocellular carcinoma and neoplastic liver nodules increased significantly with AMAQ dosage in treated rats, and the frequency of tubular cell adenomas and renal adenocarcinomas increased with increasing dosage in AMAQ-treated male rats. Although the incidence of pituitary adenomas was also significantly increased in AMAQ-treated male rats, the validity of these results was questioned based on past experience in this laboratory. The incidence of liver tumors in female mice that received AMAQ was significantly higher than that in control female mice, but there were no other significant associations between tumor incidence and drug treatment in this species. AMAQ was nephrotoxic to male mice, and kidney adenocarcinomas were found in two of these animals. It is concluded that AMAQ is carcinogenic for male and female Fischer 344 rats and female B6C3F₁ mice under the conditions of this study. (22 refs)

- 79-6793 Ornithine Decarboxylase Activity and DNA Synthesis After Treatment of Cells in Culture with 12-O-Tetradecanoylphorbol-13-acetate. (Eng) O'Brien, T. G. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Lewis, M. A.; Diamond, L. *Cancer Res* 39(11): 4477-4480; 1979.

The ability of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) to induce the enzyme ornithine decarboxylase (ODC) and to stimulate DNA synthesis was studied in four different cell types in vitro. The effects of this agent on each cell type differed as follows: (a) in hamster embryo cells, TPA induced ODC but had no effect on DNA synthesis; (b) TPA induced ODC and stimulated DNA synthesis in BALB/c 3T3 mouse cells; (c) TPA did not induce ODC in human fibroblasts but did stimulate DNA synthesis; and (d) TPA induced neither ODC nor DNA synthesis in rat embryo fibroblasts. In contrast, ODC was induced and DNA synthesis was stimulated in all cell types by fresh serum-containing medium. Treatment of the cells with a combination of fresh medium and TPA resulted in an approximate summation of the effects of treatment with each agent alone. These results emphasize the differences in the response of various cells to TPA. They also show that at least in some cells the induction of ODC and stimulation of DNA synthesis following TPA treatment can be regulated independently. (21 refs)

- 79-6794 Regulation of Normal Differentiation in Mouse and Human Myeloid Leukemic Cells by Phorbol Esters and the Mechanism of Tumor Promotion. (Eng) Lotem, J. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Sachs, L. *Proc Natl Acad Sci USA* 76(10): 5158-5162; 1979.

In one clone of mouse myeloid leukemic cells (MG1'D* clone 7-M18), 12-O-tetradecanoylphorbol-13-acetate (TPA: 1 µg/ml) induced normal cell differentiation by inducing the production of MG1 (normal protein inducer of differentiation to macrophages or

granulocytes) activity. TPA induced rosettes (mainly Fc), immune phagocytosis (Fc and C3), lysozyme, and morphological differentiation. Other MGI⁺D⁺ or MGI⁺D⁻ clones were not induced to differentiate by TPA. In an MGI⁺D⁻ clone, TPA induced cell susceptibility to externally added MGI but not to lipopolysaccharide or dexamethasone. TPA also induced differentiation in a human myeloid leukemic cell line (HL-60), with the induction of MGI activity and enhanced susceptibility to added MGI. The seeding of normal mouse bone marrow cells with TPA resulted in cluster formation due to the induction of MGI activity. When added together with MGI, TPA increased the number of macrophage and granulocyte colonies and clusters in the marrow cells. The use of different phorbol esters showed that this enhancing effect on MGI activity paralleled tumor-promoting ability. The activity of MGI was not replaced by epidermal or fibroblast growth factor (0.1-1 $\mu\text{g/ml}$) or dexamethasone (0.4 $\mu\text{g/ml}$). The results indicate that a tumor promoter such as TPA can induce the production of and increase cell susceptibility to a normal regulator of cell multiplication and differentiation. Clonal differences in the response to TPA may explain differences in tumor-promoting activity in different tissues and genetically different animals. (38 refs)

- 79-6795 Collagenase Production by Synovial Fibroblasts Treated with Phorbol Myristate Acetate. (Eng) Brinkerhoff, C. E. (Dept. Medicine, Connective Tissue Disease Section, Dartmouth Medical Sch., Hanover, NH 03755); McMillan, R. M.; Fahey, J. V.; Harris, E. D. *Arthritis Rheum* 22(10): 1109-1116; 1979.

Rabbit synovial fibroblasts were treated with the tumor promoter phorbol myristate acetate (PMA: 0.01 $\mu\text{g/ml}$), and a series of resultant intracellular events were measured. Ten min after the addition of PMA, there was a temporary increase in the intracellular cyclic AMP level, followed by a transient decrease in ³H-thymidine incorporation into DNA. After 24 hr, the prostaglandin E₂ level was increased (from approx 20 ng/mg cell protein prior to 24 hr to 500 ng). Negligible amounts of collagenase were released into the medium during the first 24 hr of PMA exposure, but there was a sudden increase after 42-48 hr; the amount was sufficient to degrade more than 250 μg collagen fibril/hr/mg cell protein at 37 C. Aspirin or indomethacin treatment (10^{-4} - 10^{-6} M for aspirin and 10^{-6} - 10^{-8} M for indomethacin) abolished prostaglandin E₂ production but did not affect the collagenase levels. Enzyme production was associated with cessation of cell proliferation, measured by protein content/culture and cell number. A long lag period between PMA treatment and the appearance of collagenase in the culture medium suggests that this system may be useful for detailed studies concerning the intracellular events leading to the induction of collagenase production by these cells. (36 refs)

- 79-6796 Enhancing Effect of Phorbol Esters on Induction of Differentiation of Mouse Myeloid Leukemia Cells by Human Urinary Protein and Lipopolysaccharide. (Eng) Nakayasu, M. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan); Shoji, M.; Aoki, N.; Sato, S.; Miwa, M.; Sugimura, T. *Cancer Res* 39(11): 4668-4672; 1979.

12-O-Tetradecanoylphorbol-13-acetate (TPA), a potent tumor promoter in mouse skin, enhanced differentiation of cultured mouse myeloid leukemia cells (M1) induced by human urinary protein or by lipopolysaccharide from *Salmonella typhosa*. TPA (in varying concentrations) enhanced differentiation of all the markers tested, such as phagocytosis, Fc rosette formation,

lysozyme activity, and morphological alteration. Other potent tumor-promoting macrocyclic plant diterpenes also enhanced the induction of differentiation, but non-tumor-promoting diterpenes did not. These findings were in marked contrast with generally accepted findings on the inhibitory effect of 12-O-tetradecanoylphorbol-13-acetate on terminal differentiation observed in other cell culture systems, but were consistent with results observed in certain leukemia cells. (37 refs)

- 79-6797 Tumor Promoters Induce Changes in the Chick Embryo Fibroblast Cytoskeleton. (Eng) Rifkin, D. B. (Dept. Cell Biology, New York Univ. Medical Center, New York, NY 10016); Crowe, R. M.; Pollack, R. *Cell* 18(2): 361-368; 1979.

The effect of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) on the actin-containing elements of the cytoskeleton of chick embryo fibroblasts (CEF) was examined. TPA at concentrations as low as 7.3×10^{-10} M induced a reversible change in the cytoskeleton, as visualized by indirect immunofluorescence using anti-actin antibodies. Cells incubated with TPA lost the ordered actin-containing structures found in normal cells and resembled Rous sarcoma virus-transformed cells in that the immunofluorescent actin pattern was diffuse. The TPA effects were both dose- and time-dependent. TPA analogs that are inactive as tumor promoters did not induce cytoskeletal changes at the concentrations tested, while a second tumor promoter, PDD, did cause alterations in actin-containing structures. The action of TPA required de novo synthesis of both RNA and protein. The direct cytoskeletal changes were neither plasmin-dependent nor subject to inhibition by incubating the cells with high levels of protease inhibitors during the exposure to TPA. However, plasminogen did increase the sensitivity of cells to TPA. (63 refs)

- 79-6798 Epidermal Prostaglandins After Topical Application of a Tumor Promotor. (Eng) Bresnick, E. (Vermont Regional Cancer Center, Univ. Vermont Coll. Medicine, Burlington, VT 05401); Meunier, P.; Lamden, M. *Cancer Lett* 7(2/3): 121-125; 1979.

12-O-Tetradecanoyl-13-acetate (TPA: 10 μg in acetone) was applied to the shaved backs of CD-1 mice to determine the effect of topical treatment on epidermal prostaglandins. The mice were killed 1-48 hr later, and epidermal prostaglandins were analyzed by radioimmunoassay. The prostaglandin E₂ (PGE₂) level was elevated almost 10-fold at 24 hr after a single application of TPA compared with control levels (2.20 vs 0.23 ng PGE₂/ μg DNA). At 12 and 48 hr after application, the epidermal PGE₂ concentration was 1.50 ng/ μg DNA. Prostaglandin F_{2 α} (PGF_{2 α}) was also significantly elevated over control values by 12 hr (0.19 vs 0.06 ng PGF_{2 α} / μg DNA) but by 48 hr, the PGF_{2 α} concentration had returned to control levels. The increase in the PGE concentration represents one of the earliest effects of TPA observed in the mouse system. The results support the hypothesis that tumor promoters exert part or all of their action through the intervention of PGE₂. (19 refs)

- 79-6799 Mechanism of Tumor Promoter Inhibition of Cellular Binding of Epidermal Growth Factor. (Eng) Lee, L. S. (Div. Environmental Science and Cancer Center, Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., 701 W. 168th St., New York, NY 10032); Weinstein, I. B. *Proc Natl Acad Sci USA* 76(10): 5168-5172; 1979.

The mechanism of 12-O-tetradecanoylphorbol-13-acetate (TPA) inhibition of cellular binding to epidermal growth factor (EGF) was investigated in several cell lines. Exposure of HeLa, mouse 3T3, xeroderma pigmentosum (XP), and rat liver K22 cells to TPA (33 nanograms/ml) resulted in a 50%-90% reduction in the cellular binding of ^{125}I -EGF. The other four cell cultures examined (CHO, B16, HTC, and CEF) had negligible levels of EGF receptors in the absence of TPA, so no significant effect of TPA on EGF binding could be detected. In HeLa cells, TPA also accelerated the loss of previously bound EGF from cells. The released EGF was recovered largely intact in the medium, which indicates that TPA does not induce increased proteolysis or increased cellular internalization and degradation of EGF. TPA inhibition of EGF binding and TPA-induced release of prebound EGF were much greater at 22 C and 37 C than at 4 C. Cells grown in TPA for ≥ 1 day escape or become refractory to TPA inhibition of EGF binding. These results suggest that TPA inhibits EGF binding indirectly by altering the conformation of or inducing the clustering of EGF receptors. (39 refs)

- 79-6800 Effects of 12-O-Tetradecanoylphorbol-13-acetate and Mezerein on Epidermal Ornithine Decarboxylase Activity, Isoproterenol-stimulated Levels of Cyclic Adenosine 3':5'-Monophosphate, and Induction of Mouse Skin Tumors In Vivo. (Eng) Mufson, R. A. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, 701 W. 168th St., New York, NY 10032); Fischer, S. M.; Verma, A. K.; Gleason, G. L.; Slaga, T. J.; Boutwell, R. K. *Cancer Res* 39(12): 4791-4795; 1979.

The tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) and the antileukemic agent mezerein, plant diterpene esters with certain structural similarities, were applied topically to mouse skin [varying doses of 1.7 or 17 nanomoles (nm), 0.34 or 3.4 nm, and/or 8.5 nm tested in some or all experiments]. The compounds were equipotent on a molar basis in inducing hyperplasia, inflammation, and ornithine decarboxylase activity, as well as in reducing cyclic adenosine 3':5'-monophosphate accumulation in response to β -adrenergic stimulation. In contrast, mezerein was much less effective as a tumor promoter; TPA at 8.5 nm/application yielded 78-fold more tumors than did 8.5 nm mezerein/application to similarly initiated (0.1 μm dimethylbenz(a)anthracene) SENCAR mice. The superiority of the phorbol ester was nearly as great in CD-1 mice. These results suggest that although the induction of hyperplasia and ornithine decarboxylase activity may be necessary components of the carcinogenic process, they are not sufficient; TPA must accomplish an essential event not accomplished by mezerein. (32 refs)

- 79-6801 Tumour Promoters Enhance Anchorage-independent Growth of Adenovirus-transformed Cells Without Altering the Integration Pattern of Viral Sequences. (Eng) Fisher, P. B. (Cancer Center/Inst. Cancer Res., Div. Environmental Sciences, Dept. Microbiology, Columbia Univ., Coll. Physicians and Surgeons, New York, NY 10032); Dorsch-Hasler, K.; Weinstein, I. B.; Ginsberg, H. S. *Nature* 281(5732): 591-594; 1979.

The effect of 12-O-tetradecanoylphorbol-13-acetate (TPA) on the acquisition of anchorage-independent growth (growth in soft agar) by adenovirus type 5 (Ad 5)-transformed secondary rat embryo (RE) cells was studied. TPA appreciably enhanced the agar cloning efficiency of the Ad 5-transformed, but not untransformed, RE cells. The optimal effect was achieved with 3 ng/ml TPA, a half-max effect being achieved with 1 ng/ml. The non-tumor promoters

phorbol and 4 α -phorbol-12,13-didecanoate did not enhance growth of transformed RE cells in agar. The TPA enhancement of anchorage-independent growth was not reversible by subcloning. The av doubling times of the anchorage-independent clones were shorter and the saturation densities higher than those of normal RE cells. The changes in cell phenotype induced by TPA were not due to alterations in the extent or state of integration of Ad 5 sequences in the genome of the host cell. (24 refs)

- 79-6802 Quantitative Assessment of Generalized Epithelial Changes in Tracheal Mucosa following Exposure to 7,12-Dimethylbenz(a)anthracene. (Eng) Topping, D. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Griesemer, R. A.; Nettesheim, P. *Cancer Res* 39(12): 4823-4828; 1979.

Sequential morphological changes following brief carcinogen exposures of heterotopic tracheal transplants in rats were semi-quantitatively studied. Tracheas were exposed to 7,12-dimethylbenz(a)anthracene for 1, 2, or 4 wk; mean dosages of carcinogen were 138, 152, and 160 μg , respectively. The first two exposure levels resulted in generalized epithelial changes only; these included hyperplasia and early metaplasia, both of which regressed rapidly, and persistent atrophic alterations. No focal epithelial lesions or tumors developed. The 160 μg exposure resulted in the appearance of generalized mucosal changes with long-lasting, severe inhibition of mucus production. In addition, focal metaplastic lesions reappeared at 4 to 8 mo after exposure; and invasive carcinomas developed at 1 yr with an incidence of 9%. Overall carcinoma incidence, including carcinoma in situ, was 15%. These studies emphasize the importance of the duration of carcinogen exposure and demonstrate the emergence of focal lesions when effective carcinogenic exposures are used. The possible significance of epithelial atrophy in the pathogenesis of cancer is discussed. (24 refs)

- 79-6803 Effects of Prostaglandins and Some Anti-inflammatory Drugs on the Binding of 7,12-dimethylbenz(a)anthracene to the DNA of Murine Epidermal Cells in Culture. (Eng) Shoyab, M. (Meloy Lab., Inc., 6715 Electronic Drive, Springfield, VA 22151). *Cancer Lett* 7(1): 155-162; 1979.

The effects of prostaglandins and some anti-inflammatory drugs such as acetylsalicylic acid, flufenamic acid, indomethacin, and flucinolone acetone (FA) on the binding of [^3H]7,12-dimethylbenz(a)anthracene (DMBA) to DNA of murine epidermal cells were investigated. Prostaglandin E_1 and Prostaglandin E_2 significantly inhibited the binding of DMBA to murine epidermal cells (MEC) DNA, while Prostaglandin $\text{F}_{1\alpha}$ and Prostaglandin $\text{F}_{2\alpha}$ did not affect the binding. Salicylic acid and flufenamic acid also did not alter the binding, whereas, indomethacin and FA lowered the binding. (36 refs)

- 79-6804 Biochemical Basis for Cytotoxicity of 7,12-Dimethylbenz(a)anthracene in Rat Liver Epithelial Cells. (Eng) Iype, P. T. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD 21701); Tomaszewski, J. E.; Dipple, A. *Cancer Res* 39(12): 4925-4929; 1979.

The effects of 7,12-dimethylbenz(a)anthracene (DMBA) on a normal liver epithelial cell line, NRL 11, and on a hepatocellular car-

cinoma cell line, HL 5, were compared. The cells were incubated with DMBA (0.001, 0.01, 0.1 or 1.0 $\mu\text{g/ml}$), and the relative plating efficiency was determined. At concentrations ≥ 0.01 $\mu\text{g/ml}$, DMBA dramatically reduced survival of normal cells, whereas, even at 1.0 $\mu\text{g/ml}$, it only marginally inhibited growth of the hepatoma cell line. The cytotoxicity was abrogated by coincubation of NRL 11 cells with 7,8-benzoflavone, which inhibits DMBA metabolism. The binding of DMBA metabolites to DNA was measured in each cell line after a 24 hr incubation with 0.05 $\mu\text{g/ml}$ DMBA. The binding in each line was low (4.1 and 5.6 $\mu\text{mol/mol}$ DNA phosphorus for HL 5 and NRL 11, respectively). Chromatographic analysis of the DMBA-nucleoside adducts revealed no qualitative differences between the two lines. Hepatoma cells, however, were more efficient than normal cells in generating very polar metabolites (not organic-solvent-extractable). These results suggest that the basis for the selective toxicity of DMBA may be that toxic metabolites are more efficiently conjugated or otherwise detoxified in the resistant HL 5 cultures. Several phenols were examined as the possible toxic metabolites of DMBA, but none approached the toxicity exhibited by DMBA itself. (32 refs)

- 79-6805 **Excision of DNA Damage Arising from Chemicals of Different Carcinogenic Potencies.** (Eng) Dipple, A. (NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701); Schultz, E. *Cancer Lett* 7(2/3): 103-108; 1979.

The excision of DNA-adducts generated by 7-bromomethylbenz(a)anthracene or 7-bromomethyl-12-methylbenz(a)anthracene was compared in two cell culture systems: primary C3H mouse embryo cell cultures and mouse L 929 cells in suspension culture. The cells were treated with 0.25, 0.50, 0.75, and 1.0 μM bromocompound; DNA was extracted from the treated cells and subjected to gradient centrifugation in cesium chloride. The dose-response curves for binding of each carcinogen to DNA were similar in both culture systems and, for both compounds, binding to DNA increased linearly with dose. The embryo cells were more efficient in excising DNA-bromocompound adducts than were the L 929 cells. In the embryo cells, excision was estimated at 60% and 67% for 7-bromomethylbenz(a)anthracene at 0.25 and 0.50 μM , whereas in the L 929 cells it was 25%, 24%, and 22% at 0.50, 0.75, and 1.0 μM , respectively. Similar results were found with the 12-methylbromo compound. Although the data for the different cell types yielded different relationships, for each cell line, the data for either compound followed the same relationship. Irrespective of which bromocompound was used, an av of approx 1.5% of the initial damage was removed per hr in the L cell suspensions, and 2.8% was removed per hr in embryo cell cultures. The results indicate that differences in the carcinogenic potency of the two compounds cannot be attributed to differences in the excisability of their DNA-adducts. (20 refs)

- 79-6806 **Shapes of Carcinogenic Benz(a)anthracenes: The Crystal and Molecular Structure of 1-Methylbenz(a)anthracene.** (Eng) Jones, D. W. (Sch. Chemistry, Univ. Bradford, Bradford, West Yorkshire, BD7 1DP, England); Sowden, J. M. *Cancer Biochem Biophys* 4(1): 43-47; 1979.

The crystal structure of 1-methylbenz(a)anthracene, a weak carcinogen, was determined by application of direct methods to single-crystal x-ray diffractometric data and refined by least squares to $R = 0.09$ over 845 independent reflections. Crystals are monoclinic, space group $P2_1$, with $a = 8.491(2)$, $b = 7.138(2)$, $c =$

$10.500(2)$ Å, $\beta = 95.06(01)^\circ$, $Z = 2$. As in other benz(a)anthracenes, the K-region bond C(5)-C(6) is short [1.34(1)Å]. The distinctive bay geometry, with a methyl group opposite to a hydrogen, H(12), *peri* to another hydrogen, H(11), features a long bond C(13)-C(18) = 1.47(1) Å in the bay; and the angular benz-ring is inclined at 16.5° to the mean plane of the anthracene fragment. The methyl carbon atom is 0.79 Å out of the mean molecular plane (or 0.19 Å out of the plane of the benz-ring) and the 1.50 Å long C(1)-methyl bond makes angles of 117° and 125° at C(1). (19 refs)

- 79-6807 **Covalent Binding of Polycyclic Aromatic Hydrocarbons to Adenine Correlates with Tumorigenesis in Mouse Skin.** (Eng) DiGiovanni, J. (Dept. Pharmacology, Sch. Medicine, Univ. Washington, Seattle, WA 98195); Romson, J. R.; Linville, D.; Juchau, M. R.; Slaga, T. J. *Cancer Lett* 7(1): 39-43; 1979.

The possible association between skin-tumor initiation and covalent binding of several polycyclic aromatic hydrocarbons (PAH) was studied in vitro. Epidermal homogenates from female CD-1 mice were used to convert the PAH to metabolites capable of binding covalently with nucleic acids. Poly(G) showed the greatest capacity to bind covalently with the PAH, but there was no correlation between binding to poly(G) and tumorigenicity for mouse skin. Covalent binding to poly(A) did, however, correlate well with values obtained for binding to DNA and mouse skin tumorigenicity. The order of binding to poly(A) was: 7,12-dimethylbenz(a)anthracene > benzo(a)pyrene > dibenz(a,h)anthracene > dibenz(a,c)anthracene. It is suggested that binding to adenine may be critical in terms of PAH carcinogenesis in mouse skin. (23 refs)

- 79-6808 **The Induction of Sister Chromatid Exchanges by Dihydrodiols Derived from 7,12-Dimethylbenz(a)anthracene and 3-Methylcholanthrene.** (Eng) Pal, K. (Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England); Grover, P. L.; Sims, P. *Cancer Lett* 7(1): 45-49; 1979.

The induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary (CHO) cells by the polycyclic hydrocarbons, 7,12-dimethylbenz(a)anthracene (DMBA) and 3-methylcholanthrene (MCA) and some of the related dihydrodiols was investigated. Increased numbers of SCE occurred in the chromosomes of cells exposed to non-K-region dihydrodiols. The most active compounds were the 3,4-dihydrodiol of DMBA and the 7,8- and 9,10-dihydrodiols of MCA; the parent hydrocarbons and their corresponding K-region dihydrodiols were relatively less active. The results are consistent with those of other studies that suggest that the metabolic activation of both hydrocarbons proceeds through the conversion of non-K-region dihydrodiols into vicinal diol-epoxides. (7 refs)

- 79-6809 **Binding of Epidermal Growth Factor to Primary and Permanent Cultures of Mouse Epidermal Cells: Inhibition by Tumor-promoting Phorbol Esters.** (Eng) Murray, A. W. (Sch. Biological Sciences, Flinders Univ., South Australia 5042, Australia); Fusenig, N. E. *Cancer Lett* 7(2/3): 71-77; 1979.

The binding of epidermal growth factor (EGF) to primary and permanent cultures of mouse epidermal cells was studied with and

without the addition of tumor-promoting phorbol esters. EGF bound to all three epidermal cell types tested: primary epidermal cell cultures (PEC), a mouse epidermal cell line transformed in vitro by 7,12-dimethylbenz(a)anthracene (PDV), and a spontaneously transformed cell line (HEL/37). Binding of EGF to all cells tested was strongly inhibited by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and phorbol-12,13-didecanoate, which are powerful tumor-promoting agents, but not by their nonpromoting derivatives, 4-O-methyl-tetradecanoylphorbol-13-acetate or 4 α -phorbol-12,13-didecanoate, respectively. The TPA concentration required for 50% of the max inhibition was 2.3×10^{-9} M. Binding was inhibited <7% by a 30-fold excess of other peptide hormones, indicating that the interaction of TPA with receptor sites was specific for EGF. Preliminary results of studies of the nature of this interaction suggest that it is noncompetitive. The present results suggest that the biological activity of phorbol esters in epidermal cultures may be significant for their mechanism of action in vivo. (25 refs)

- 79-6810 Mechanism of Ovarian Carcinogenesis: Effect of 7,12-Dimethylbenz(a)anthracene Administration on Intrasplenic Ovarian Grafts in Unilaterally Ovariectomized C3HeB/Fe Mice. (Eng) Armuth, V. (Weizmann Inst. Science, Rehovot, Israel); Berenblum, I. *J Natl Cancer Inst* 63(4): 1047-1050; 1979.

The mechanism of chemically induced ovarian neoplastic transformation was investigated. A single po administration of 7,12-dimethylbenz(a)anthracene (DMBA) 2 wk after intrasplenic grafting of ovarian tissue in unilaterally ovariectomized C3HeB/Fe mice resulted in a high tumor incidence (47%) in the grafted tissue, with only one tumor (3%) in the orthotopic ovary. No tumors occurred in unilaterally ovariectomized controls that received intrasplenic ovarian tissue grafts without subsequent DMBA administration, nor did tumors develop in response to DMBA treatment in mice with both ovaries in situ and no grafted tissue in the spleen. The results indicate that some local change caused by the grafting procedure rendered the tissues more sensitive to the action of DMBA and/or more responsive to gonadotropic stimulation. (20 refs)

- 79-6811 Inhibition of Preovulatory Gonadotropin Secretion and Stimulation of Prolactin Secretion by 7,12-Dimethylbenz(a)anthracene in Sprague-Dawley Rats. (Eng) Kerdelhue, B. (Laboratoire des Hormones Polypeptidiques, Centre Natl. de la Recherche Scientifique, 91190 Gif-sur-Yvette, France); El Abed, A. *Cancer Res* 39(11): 4700-4705; 1979.

Serum luteinizing hormone, follicle-stimulating hormone, prolactin, thyroid-stimulating hormone, growth hormone and hypothalamic luteinizing hormone and thyroliberin contents were measured at given times of the estrous cycle in dimethylbenz(a)anthracene (DMBA)-susceptible Sprague-Dawley rats and in DMBA-resistant Wistar rats for periods up to the appearance of the first mammary tumors in DMBA-susceptible animals. Tumors usually appeared with approx 100% incidence around the 14th to 15th estrous cycle after DMBA treatment in Sprague-Dawley rats. Hormonal determinations were done by using groups of 4-day cycling rats of both strains which were given DMBA (15 mg) or the vehicle (sesame oil) on a single diestrus I at around 55 days of life. Animals were sacrificed by decapitation without previous anesthesia on the morning and afternoon of proestrus and estrus during the 5th and 11th estrous cycles after treatment. In Sprague-Dawley female rats,

DMBA significantly inhibited luteinizing hormone and follicle-stimulating hormone surges and stimulated the prolactin surge on the afternoon of proestrus at any estrous cycle after treatment (the timing of preovulatory surges was the same in both strains for any hormone at other times of the estrous cycle). In contrast, Wistar rats did not show deranged preovulatory or basal prolactin and gonadotropin release after treatment with the carcinogen; in addition, no difference was found for any other hormone at any time tested. These results show that there is a specific and transient hormonal deregulation in a DMBA-susceptible strain of rats. Inasmuch as the hormonal imbalance was essentially the same throughout the induction period, an early and persistent alteration in centers implicated in the hormonal cyclicality of the hypothalamopituitary axis must result from DMBA treatment. (17 refs)

- 79-6812 Transformation of Hamster Fetal Cells by Nitrosated Pesticides in a Transplacental Assay. (Eng) Quarles, J. M. (Dept. Medical Microbiology and Immunology, Coll. Medicine, Texas A & M Univ., College Station, TX 77843); Segal, M. W.; Schenley, C. K.; Lijinsky, W. *Cancer Res* 39(11): 4525-4533; 1979.

The transplacental host-mediated hamster cell culture assay was used to test a series of solvents, control chemicals, and pesticides and their corresponding N-nitroso derivatives for transforming activity. In addition to testing for morphological transformation, growth of cells suspended in 0.3% agar and tumorigenicity in nude mice were also determined. Since no transforming activity was detected during examination of approx 38,000 colonies from cultures obtained from untreated animals nor from the 22,000 colonies of cells from animals treated with only solvents, the possible occurrence of spontaneous or solvent-induced transformation did not pose any significant problem. Cells exhibiting transformed morphology, growth in soft agar, and tumorigenicity in nude mice were obtained from fetal cell cultures of pregnant hamsters treated with several known carcinogens [eg, diethylnitrosamine, nitrosomethylurethane, and 7,12-dimethylbenz(a)anthracene] and all the nitrosated pesticides tested, including the N-nitroso derivatives of carbaryl, carbofuran, Baygon, Landrin, Bux Ten, methomyl, and aldicarb. The parent pesticides were found to be nontransforming in this study, with the exceptions of infrequent morphological transformation without growth in soft agar or tumorigenicity by Landrin and Bux Ten. The transplacental host-mediated assay was shown to be useful in determining transforming activity in a variety of chemicals of known and unknown carcinogenicity especially when used in conjunction with the soft agar assay. (31 refs)

- 79-6813 Studies with Chlorinated Dibenzo-*p*-Dioxins, Polybrominated Biphenyls, and Polychlorinated Biphenyls in a Two-Stage System of Mouse Skin Tumorigenesis: Potent Anticarcinogenic Effects. (Eng) Berry, D. L. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Slaga, T. J.; DiGiovanni, J.; Juchau, M. R. *Ann NY Acad Sci* 320: 405-414; 1979.

The ability of chlorinated dibenzo-*p*-dioxins, polybrominated biphenyls (PBBs), and polychlorinated biphenyls (PCBs) to modify tumor initiation in a mouse skin assay was studied in female CD-1-mice. Topical 12-O-tetradecanoylphorbol-13-acetate (TPA) caused marked inflammation and increased layers of intrafollicular epidermis (IFE). 2,3,7,8-Tetrachlorodibenzo-

p-dioxin (TCDD) caused some increase in the number of cells in the IFE; PCBs and PBBs did not affect the IFE, and 2,7-dichlorodibenzo-*p*-dioxin (DCDD) and 3,4',3',4'-tetrachloroazobenzene (TCAB) did not cause increased thickening of the IFE. The two biphenyls and TCDD did not promote the development of skin tumors following 7,12-dimethylbenz(a)anthracene (DMBA) initiation. Aroclor 1254 and TCDD were very weak tumor initiators, but they decreased DMBA initiation by 45% and 93%, respectively. DCDD slightly inhibited DMBA initiation, and TCAB slightly enhanced it. The inhibition of DMBA initiation by TCDD was related to the ability of TCDD to induce epidermal monooxygenases, which are responsible for converting DMBA to a variety of hydroxylated products. TCDD pretreatment reduced the binding of subsequently applied DMBA to epidermal DNA and, to a lesser extent, RNA; it had no effect on the binding of DMBA to epidermal protein. (36 refs)

PAH either had no significant effect or had a slight enhancing effect on skin tumor initiation by BP. BeP also had essentially no effect on initiation by \pm benzo(a)pyrene-7 β ,8 α -diol-9 α , 10 α -epoxide. BeP at 252 μ g showed weak tumor initiating capacity, and at 100 μ g, no tumor initiating capacity was present. When administered 2x/wk at 100 μ g, BeP had induced 2.1 papillomas per mouse at 30 wk, and 25% of the mice had carcinomas by 40 wk. A comparable response was obtained with 5 μ g BP 2x/wk. When administered at 100 μ g 2x/wk following DMBA initiation, BeP induced 4.5 papillomas per mouse at 30 wk, and there was an incidence of 45% at 40 wk. Thus, BeP is a weak complete carcinogen, a moderate tumor promoter, possibly a weak co-initiator when given with BP, and a potent anti-tumor-initiator when administered with DMBA. The anti-tumor initiating and co-initiating effects of BeP appear to be related to its ability to modify the conversion of the tumor initiator to an electrophilic intermediate(s) capable of covalently binding to DNA. BeP also induced epidermal cell proliferation, which may be related to its promoting ability. (31 refs)

79-6814 Development and Fate of Focal Epithelial Lesions in Tracheal Mucosa Following Exposure to 7,12-Dimethylbenz(a)anthracene. (Eng) Topping, D. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Griesemer, R. A.; Nettesheim, P. *Cancer Res* 39(12): 4829-4837; 1979.

Rat tracheas transplanted sc to the backs of syngeneic host animals were implanted with intraluminal pellets containing 165 μ g 7,12-dimethylbenz(a)anthracene (DMBA) for 4 wk. Groups of tracheas were examined histologically 2-12 mo after exposure. Between 2 and 4 mo, 62%-72% of the tracheas sampled contained focal lesions; this declined to 44% at 12 mo. The number of lesions per trachea (2.8-3.5 lesions/trachea) remained relatively constant between 2 and 12 mo. Metaplasias with no or minimal atypia were the most common lesions. The drop in the incidence of lesions between 4 and 12 mo was due to a decrease in the frequency of this type of lesion, indicating that it is reversible. There was a fourfold increase in the incidence of advanced lesions, from 8% at 2 mo to 36% at 12 mo. The first invasive carcinomas were observed at 4 mo; the incidence was 5%, and this incidence did not change significantly during the rest of the study. Some carcinogen-exposed transplants were examined for tumor induction over a 28-mo period. Invasive squamous cell carcinomas occurred 10-22 mo after pellet removal in 8/86 tracheas, and advanced lesions occurred in 9/86 (4 severe atypias, 2 carcinomas in situ, and 3 microinvasive carcinomas). No advanced lesions were detected in 32 tracheas obtained after 20 mo, which indicates that the trend in reduction of lesions with time seen in the serial sampling study is real. These studies indicate that a considerable number of DMBA-induced tracheal lesions remain stationary for a long period and that many others, including some advanced lesions, regress. (27 refs)

79-6815 The Effects of Weak or Non-carcinogenic Polycyclic Hydrocarbons on 7,12-Dimethylbenz(a)anthracene and Benzo(a)pyrene Skin Tumor Initiation. (Eng) Slaga, T. J. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN 37830); Jecker, L.; Bracken, W. M.; Weeks, C. E. *Cancer Lett* 7(1): 51-59; 1979.

The effects of weakly and noncarcinogenic polycyclic aromatic hydrocarbons (PAH) on skin tumor initiation by 7,12-dimethylbenz(a)anthracene (DMBA) and benzo(a)pyrene (BP) were studied in female CD-1 mice. Benzo(e)pyrene (BeP) inhibited DMBA skin tumor initiation by 84%, whereas pyrene and fluoranthene were only 50% and 34% inhibitory, respectively. These

79-6816 Neovascularization During Hamster Cheek Pouch Carcinogenesis Induced by 7,12-Dimethylbenz(a)anthracene. (Eng) Tatematsu, M. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Nakatsuka, T.; Lurie, A. G.; Rippey, R. M.; Suzuki, M.; Ito, N. *Gann* 70(5): 719-720; 1979.

The cheek pouches of 100 male golden hamsters were treated with 0.05 ml of a 0.5% 7,12-dimethylbenz(a)anthracene (DMBA) soln in mineral oil 3x/wk for 14 wk, with no application during wk 3, 7, and 11. Cheek pouches were examined histopathologically and by scanning electron microscopy after sacrifice 2-30 wk after the start of DMBA treatment. Normal cheek pouches had loose plexi of capillaries, which were relatively uniform and present in low density. Small foci of high-density plexi of small diameter capillaries (type I) were occasionally seen in DMBA-treated cheek pouches. They were most frequent at wk 4 and had disappeared by wk 14. Type III foci, highly tortuous capillary loops without terminal branches, were first seen at 6 wk and increased gradually in number and extent. After 14 wk, the capillaries became irregular and had a diameter considerably larger than normal. Histologically, mild hyperplasia was seen after wk 6, and small papillomas were found after wk 10. Squamous cell carcinomas occurred after 14 wk. Type I foci may represent repair of direct damage to blood vessels. Type III foci showed a close relationship with epithelial proliferative lesions, hyperplasia, papillomas, or carcinomas, and may represent endothelial responses to secretion of an angiogenic factor from malignant or premalignant tissues. (5 refs)

79-6817 Sialic Acid Metabolism in Rats Undergoing Chemically-induced Mammary Gland Carcinogenesis in Specific Dietary States. (Eng) Fox, O. F. (Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, Oklahoma City, OK 73104); Kishore, G. S.; Carubelli, R. *Cancer Lett* 7(5): 251-257; 1979.

The enzymes responsible for the activation, transfer, and hydrolysis of sialic acids were investigated in female Sprague-Dawley rats with mammary adenocarcinomas induced by administration of a single po dose (10 mg) of 7,12-dimethylbenz(a)anthracene. The carcinogenic process was modulated by the levels and degree of unsaturation of the dietary lipids. Tumor incidence was highest in rats fed a diet containing 20% corn oil, intermediate

in those fed a diet containing 18% coconut oil plus 2% linoleic acid, and lowest in those receiving a diet with 2% linoleic acid. Sialyltransferase and CMP-*N*-acetylneuraminic acid synthetase activities were higher in tumors than in control mammary glands. Neuraminidase activity, on the other hand, was higher in control tissue than in tumors. In addition to these tumor-related effects, comparison of the enzyme levels in mammary tissues from control animals in the three dietary groups revealed the presence of diet-related effects on sialic acid metabolism. In the livers of tumor-bearing rats, only minor changes in enzyme activities were detected. The authors speculate that the enzymatic changes observed in the control mammary tissue of rats fed a low-fat diet may reflect a biochemical environment unfavorable for the malignant transformation of mammary cells. (18 refs)

- 79-6818 Inhibition of Mammary Tumorigenesis in Carcinogen-treated Lewis Rats by Suppression of Prolactin Secretion. (Eng) Welsch, C. W. (Dept. Anatomy, Michigan State Univ., East Lansing, MI 48824); Brown, C. K.; Goodrich-Smith, M.; Van, J.; Denenberg, B.; Anderson, T. M.; Brooks, C. L. *J Natl Cancer Inst* 63(5): 1211-1214; 1979.

A total of 168 female Lewis rats were treated intragastrically with 10 mg of 7,12-dimethylbenz[a]anthracene at 56 and 63 days of age. Pituitary prolactin secretion was suppressed in half of these rats by daily sc 2-bromoergocryptine mesylate administration (CB-154: 0.4 mg/100 g body wt) from 29 to 90 days of age (series 1) and from 90 to 140 days of age (series 2). Treatment with CB-154 was initiated prior to the onset of palpable mammary carcinomas. Controls received saline injections. Inguinal mammary glands were excised from 10 control and 10 CB-154-treated rats at the cessation of saline and CB-154 treatments and examined for hyperplastic nodules (HN). The remaining rats were examined weekly for mammary carcinoma (MC) and killed at 200 days of age. The mean number of HN per rat, mean number of MC per rat, and percent of rats with MC were, respectively: series 1-controls, 0.6, 1.5, and 68; CB-154 treatment, 0.5, 1.1, and 62; series 2-controls, 10.4, 2.0, and 94; CB-154 treatment, 5.1, 1.1, and 56. The number of HN and MC was only slightly reduced in rats when prolactin was suppressed during carcinogen treatment (series 1) but markedly reduced when prolactin was suppressed after carcinogen treatment (series 2). These results provide evidence that prolactin is involved in the early development of mammary dysplasias in carcinogen-treated female Lewis rats. (19 refs)

- 79-6819 Induction, Inhibition, and Some Enzymological Properties of Aryl Hydrocarbon Hydroxylase in Fresh Mitogen-activated Human Lymphocytes. (Eng) Gurtoo, H. L. (Grace Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm Street, Buffalo, NY 14263); Parker, N. B.; Paigen, B.; Havens, M. B.; Minowada, J.; Freedman, H. J. *Cancer Res* 39(11): 4620-4629; 1979.

Basal and/or polycyclic aromatic hydrocarbon (PAH)-induced aryl hydrocarbon hydroxylase (AHH) in mitogen-activated cultured lymphocytes obtained from healthy donors was studied for the specificity of induction and inhibition and of other enzymological properties. Of the 24 chemicals tested, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), dibenz(a,h)anthracene (DBA), benz(a)anthracene (BA), 3-methylcholanthrene (3-MC), β -naphthoflavone, cholecalciferol, and DL-isoproterenol were

good inducers (inducibility ratio, >2.0). Other chemicals which produced effects ranging from inhibition to mild induction included 4-bromoflavone, α -naphthoflavone, chrysene, *p,p'*-1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane, 7,12-dimethylbenzanthracene, pyrene, DL-norepinephrine, benzo(a)pyrene, lindane, *v*-octylamine, testosterone, 2,5-diphenyloxazole, 17 β -estradiol, metyrapone, and phenobarbital. TCDD was the most potent inducer, followed by DBA \geq BA $>$ 3-MC. The data suggest that the latter four inducers could be used interchangeably as they appear to activate the common, genetically determined factors involved in the induction of AHH. The order of potency among the inhibitors was α -naphthoflavone $>$ β -naphthoflavone, followed by 2-diethylaminoethyl-2,2-diphenylvalerate, metyrapone, 1,1,1-trichloropropene oxide, and cyclohexene oxide. Depending upon the concentration used, the latter four inhibitors produced moderate inhibition to moderate stimulation; however, the inhibition pattern for the basal and the PAH-induced AHH was indistinguishable. The half-life of the enzyme during cell culture and the K_m values of the AHH in uninduced and PAH-induced cells were also similar. Thus, basal and induced AHH appear to be qualitatively similar, differing only quantitatively in comparable uninduced and PAH-induced cells. (52 refs)

- 79-6820 Bioassay of C. I. Vat Yellow 4 for Possible Carcinogenicity. (Eng) National Cancer Institute (NCI, Bethesda, MD 20014). *Natl Cancer Inst Carcinog Tech Rep Ser* (134): 106 pp.; 1979.

Results of the bioassay of C. I. vat yellow 4 (dibenzo(b,def)chrysene-7,14-dione) for the carcinogenesis testing program are reported. Groups of 50 animals of each sex were given yellow 4 in the diet at one of two dose levels. Fischer 344 rats were fed at 3,500 or 7,000 ppm for 104 wk. Male mice (B6C3F1) were given 25,000 or 50,000 ppm, and female mice (same strain) were given 12,500 or 25,000 ppm. Mice were fed for 106 wk. Survival of rats and mice was not decreased by yellow 4. In all rat groups and the female mice groups, no tumors occurred at incidences significantly higher than in the matched control groups (20 rats, 20 mice of each sex). Lymphoma incidence (44%) was higher ($p = 0.019$) in male mice given the higher dose than in the low-dose and control groups (15% incidence). Hepatomas were more frequent (22/47 at the low dose, 21/50 at the high dose) in treated male mice than in the controls (3/20). Although the human risk from yellow 4 is very low, the carcinogenic potential suggested by the increased incidences of lymphomas and hepatomas in male mice indicates that further tests may be required. (18 refs)

- 79-6821 Effect of Protein Synthesis Inhibitors on the Induction of Rat Liver Microsomal Cytochrome P-448 by 3-Methylcholanthrene. (Eng) Poole, T. W. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England); Parke, D. V. *Biochem Soc Trans* 7(5): 1109-1111; 1979.

The effects of protein-synthesis inhibitors on the induction of rat liver microsomal cytochrome P-448 by 3-methylcholanthrene (MCA: 25 mg/kg, ip) were studied. Thirty min before MCA administration, male Wistar rats received cycloheximide (CH: 2 mg/kg), actinomycin D (2 mg/kg), or α -amanitin (1 mg/kg) ip. Cytochrome P-448 induction was completely prevented by CH, which also prevented an MCA-induced decrease in ethylmorphine *N*-demethylase activity. CH only partly reversed the enhancement of ethoxycoumarin *O*-de-ethylase and biphenyl 2-hydroxylase in-

duced by MCA. Increases in enzyme activities associated with MCA treatment were not completely prevented by CH. (11 refs)

- 79-6822 Susceptibility and Resistance to Chemical Carcinogens in Inbred Syrian Hamsters. (Eng) Homburger, F. (Bio-Res. Inst., 9 Commercial Ave., Cambridge, MA 02141); Adams, R. A.; Soto, E.; Van Dongen, C. G. *Prog Exp Tumor Res* 24: 215-221; 1979.

The comparative susceptibilities of several inbred strains of hamsters to a variety of carcinogens were studied. The data indicate varying degrees of resistance and susceptibility to both spontaneous and induced malignancies, and these appear to be governed by genetic factors. To study carcinogens for which the mammary gland is a target, the female BIO 15.16 hamster would be the preferred model, whereas for intestinal cancer the BIO 15.16 or BIO 87.20 male would be preferred. The BIO 15.16 hamster is a good model for cigarette smoke-induced cancer of the larynx, and bladder cancer would best be studied using one of the inbred lines responding to β -naphthylamine feeding with urothelial carcinomas (eg, the BIO 87.20 male). Hybrids of two susceptible BIO lines (BIO 15.16 \times BIO 87.20) appear to be as susceptible as the parental strains to sc methylcholanthrene; these hybrids might prove to be sturdy, rapidly breeding test animals for carcinogenesis studies. (13 refs)

- 79-6823 Reduction in the Formation of Carcinogen-induced Transformed Foci by Penicillin G Sodium in the C3H/10T_{1/2} CL8 Cell Line. (Eng) Bertram, J. S. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY 14263). *Cancer Lett* 7(5): 289-298; 1979.

As part of a continuing effort to improve an in vitro assay system for malignant transformation that employs the C3H/10T_{1/2} CL8 cell line, experiments were carried out to determine whether Gentamicin could be substituted for the combination of penicillin (100 IU/ml) and streptomycin (50 μ g/ml) that has hitherto been used to reduce the occurrence of bacterial contamination. In preliminary studies, the penicillin component of the mixture had been discovered to cause a reduction in the number of transformed foci developing after exposure of cells to 3-methylcholanthrene, 7,12-dimethylbenzanthracene and x-rays. This reduction was found to be dose dependent; 500 IU/ml virtually eliminated transformation, while 100 IU/ml caused an approx 50% decrease in the number of foci. This effect did not appear to be due to overt toxicity and was largely reversible on removal of the antibiotic. Gentamicin (25 μ g/ml) caused no reduction in the formation of transformed foci when compared with cultures maintained in antibiotic-free medium. Gentamicin also offers the advantages of chemical stability, a wider spectrum of antibacterial activity in comparison with penicillin/streptomycin and is active against many mycoplasma. It is suggested that future studies with this cell line should ideally be performed without antibiotics or should employ Gentamicin for antibacterial protection. (17 refs)

- 79-6824 Carcinoma Induction by 3-Methylcholanthrene in Hamster Tracheal Tissue Implanted in Syngeneic Animals. (Eng) Craighead, J. E. (Dept. Pathology, Univ. Vermont Coll. Medicine, Burlington, VT 05401); Mossman, B. T. *Prog Exp Tumor Res* 24: 48-60; 1979.

The induction of neoplasms in BIO 15.16 strain Syrian golden hamsters by the implantation of hamster tracheal organ cultures exposed to 3-methylcholanthrene (MC) adsorbed onto particles of asbestos and Fe₂O₃ was studied. Cysts often developed after implantation of such organ cultures, the structures appearing to have formed from outgrowths of epithelial cells that proliferated from the margins of the explants. The grafts retained their original structure and mucociliary epithelial lining. Neoplasms developed in implanted tracheal organ cultures 3-17 mo after exposure to MC (0.6-10 μ g/graft). All but 13 of the 67 tumors studied were carcinomas, the exceptions exhibiting features of well-differentiated fibrosarcomas. Cytological features of neoplastic transformation were frequently observed adjacent to the presumed sites of epithelial origin of the neoplasms, and transitions from carcinoma in situ to frankly invasive tumor were commonly demonstrated. In implants not developing tumors, both focal and extensive areas of squamous metaplasia were observed, as were other cytological atypias. Most of the carcinomas were made up of poorly differentiated polygonal cells, although occasional epidermoid, adeno-, and small cell carcinomas were found. (19 refs)

- 79-6825 Use of Hamster Tracheal Organ Cultures for Assessing the Cocarcinogenic Effects of Inorganic Particulates on the Respiratory Epithelium. (Eng) Mossman, B. T. (Dept. Pathology, Univ. Vermont Coll. Medicine, Burlington, VT 05401); Craighead, J. E. *Prog Exp Tumor Res* 24: 37-47; 1979.

Intratracheal instillation of polycyclic hydrocarbons bound to 'carrier' particulates induces respiratory tract neoplasms in laboratory animals. To elucidate the respiratory epithelial changes caused by carcinogens and selected inorganic particles, tracheal organ cultures were prepared from female Syrian golden hamsters (BIO 15.16 strain). Explants were exposed to 3-methylcholanthrene (3-MC) coated onto either ferric oxide or crocidolite asbestos. Control tissues were treated with particulates without 3-MC. At intervals of 24 and 72 hr and 1, 2, 3, and 4 wk, the cultures either were examined morphologically or implanted sc into syngeneic hamsters. Greater amounts of 3-MC were required to induce tumors with Fe₂O₃ than with asbestos. Nine fibrosarcomas and 13 carcinomas were induced in all. Dose-response determinations indicated a degree of precision in these studies unattainable in whole animal models of respiratory carcinogenesis. (18 refs)

- 79-6826 Methylcholanthrene-induced Metastatic Mammary Carcinoma in Several Inbred Hamster Strains. (Eng) Adams, R. A. (Bio-Res. Inst., 9 Commercial Ave., Cambridge, MA 02141); Homburger, F.; Russfield, A. B.; Soto, E. *Prog Exp Tumor Res* 24: 408-413; 1979.

The administration of multiple small doses (total dose 200 mg over a 17-wk period) methylcholanthrene by stomach tube resulted in the induction of metastasizing mammary gland carcinoma in the females of 10 BIO inbred Syrian hamster strains. The incidence of primary induced mammary carcinoma, predominantly papillary cystadenocarcinoma, varied from 39% to 95%; 5 strains had mammary carcinoma incidences above 80%. Grossly observed and histologically verified metastases to one or more lymph nodes were noted in 10-79% of the 142 female hamsters with mammary gland carcinoma (av 42%), multiple lymph node involvement being by far the most frequent finding. Metastasis to the lung, with or without lymph node metastases, was observed in about 13% of the hamsters. Hamsters with mammary gland carcinoma survived 25-

33 wk following the initiation of carcinogen exposure, as compared to 89-100 wk for controls given corn oil only. These high incidences of metastatic mammary carcinoma induced in a relatively short time suggest that some of the inbred BIO hamster strains provide excellent models of metastatic breast cancer. (8 refs)

- 79-6827 Comparison of the Skin Tumor Initiating Activity of 3-methylcholanthrene and 3,11-Dimethylcholanthrene in Mice. (Eng) Slaga, T. J. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN 37830); Gleason, G. L.; Hardin, L. *Cancer Lett* 7(2/3): 97-102; 1979.

The skin tumor initiating activities of 3-methylcholanthrene (3-MC) and 3,11-dimethylcholanthrene (3,11-DMC) were compared in female Sencar mice. Groups of 30 7- to 9-wk-old animals received a single topical application of 100 nmol of 3-MC or 3,11-DMC followed 1 wk later by applications of 12-O-tetradecanoylphorbol-13-acetate (TPA: 2 µg 2x/wk). After 16 wk of TPA promotion, 3-MC had induced tumors in 92% of the mice, with an av of 4.5 papillomas/mouse; 3,11-DMC induced tumors in 10% of the mice, with an av of 0.2 papillomas/mouse. The only difference between 3-MC and 3,11-DMC is the substitution of a methyl group in position 11, which is part of the K-region or the peri position. These results suggest that an unhindered peri position adjacent to an angular benzene ring is necessary for carcinogenic activity. (33 refs)

- 79-6828 Metabolism and DNA Binding of 3-Methylcholanthrene. (Eng) Eastman, A. (Dept. Biochemistry, Vermont Regional Cancer Center, Burlington, VT 05405); Bresnick, E. *Cancer Res* 39(11): 4316-4321; 1979.

Rat liver microsomes metabolize 3-methylcholanthrene (3MC) to oxygenated forms which alkylate DNA. Analysis of the DNA-bound products by high-pressure liquid chromatography revealed at least 13 deoxyribonucleoside adducts. The two major adducts contained guanine and had fluorescence spectra consistent with saturation at carbon atoms 7, 8, 9, and 10. Microsome-catalyzed binding of 3MC to double-stranded and single-stranded DNA yielded quantitatively similar patterns, suggesting that specific adducts do not arise from orientation of the hydrocarbon into the DNA helix prior to metabolic activation. The adducts produced in vitro varied with time of incubation; the more polar adducts appeared after longer time periods. Seven of the adducts were also detected in DNA from the lung and liver of C57BL/6J mice that had been given iv injections of 500 µCi [³H]-3MC; the relative amounts of each adduct most closely resembled the pattern which was observed after long incubation of microsomes with DNA in vitro. Microsome-mediated metabolism of [³H]-3MC was also studied. 2-Hydroxy-3-methylcholanthrene, rather than 1-hydroxy-3-methylcholanthrene, was the major metabolite, the latter being barely undetectable. Other metabolites included *trans*-9,10- and *trans*-11,12-dihydrodiols and a variety of unidentified derivatives which may bear modifications on either the saturated five-membered ring or on the 3-methyl group. These derivatives were reincubated with microsomes and DNA. After such incubations, seven 3MC metabolites bound to DNA with higher efficiency than did the parent hydrocarbon; *trans*-9,10-dihydrodiol had the highest efficiency in this regard. The other six metabolites which subsequently showed high binding efficiency appeared to be derivatives on carbon 1, carbon 2, or the 3-methyl. Although the major binding to DNA may be through a vicinal diol-epoxide, the complexity surrounding the aliphatic five-membered

ring probably also contributes to the large number of adducts detected. (32 refs)

- 79-6829 Benzo(a)pyrene Antibody Inhibition of Benzo(a)pyrene-induced Mutagenesis. (Eng) Tompa, A. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE 68105); Curtis, G.; Ryan, W.; Kuszynski, C.; Langenbach, R. *Cancer Lett* 7(2/3): 163-169; 1979.

The in vitro effect of a benzo(a)pyrene (BP) antibody on the mutagenic and cytotoxic activity of BP was investigated in a cell-mediated mutagenesis assay. Chinese hamster V79 cells, which cannot metabolically activate BP, were incubated with rat embryo fibroblasts or rat lung epithelial cells with and without BP antibody γ-globulin. Mutagenicity in the V79 cells was measured by induction of resistance to thioguanine and/or ouabain. In the fibroblast-mediated system, BP induced 36 mutants/10⁶ survivors; the presence of the BP antibody reduced the mutation frequency to 13 mutants/10⁶ survivors. In the lung cell-mediated system, BP induced 19 ouabain-resistant mutants/10⁶ and 20 thioguanine-resistant mutants/10⁶ survivors. In the presence of BP antibody, the mutation frequency was six ouabain-resistant mutants/10⁶ and four thioguanine-resistant mutants/10⁶ survivors. BP antibody reduced BP cytotoxicity in both cell-mediated systems. The mechanism of this antibody protection is not known. It is possible that the antibody alters the types of BP metabolites formed or binds to activated intermediates, thereby limiting their interaction with macromolecules in the V79 cells. The level of antibody in vivo may be sufficient to bind an environmental carcinogen encountered in µg/day quantities but not in mg/day quantities. (21 refs)

- 79-6830 Induction of Aryl Hydrocarbon Hydroxylase in Primary Cultures of Type II Alveolar Lung Cells and Binding of Metabolically Activated Benzo(a)pyrene to Nuclear Macromolecules. (Eng) Teel, R. W. (Dept. Physiology and Pharmacology, Sch. Medicine, Loma Linda Univ., Loma Linda, CA 92350). *Cancer Lett* 7(6): 349-355; 1979.

Aryl hydrocarbon hydroxylase (AHH) induction and binding of benzo(a)pyrene (BP), 3-methylcholanthrene (3-MC), and 9,10-dimethyl 1,2-benzanthracene (DMBA) to nuclear macromolecules was studied in alveolar-like structures composed of fetal rat cells resembling type II alveolar pneumonocytes. Cultures were exposed to one of the test compounds (2 µg/ml) for 24 hr and assayed for AHH activity at various times up to 30 days after exposure. With BP, AHH activity reached a peak in 6-day cultures and remained stable over a period of 12 days. There was an abrupt decline in AHH activity after 18 days. In 7-day-old cultures, AHH activity induced by DMBA was 20% of that induced by BP, and 3-MC-induced AHH activity was only 6% that of BP. Six-day cultures were incubated with [³H]BP for 24 hr at 2 µCi/ml culture medium, and the binding of BP metabolites to DNA, histone, and nonhistone proteins was determined. Although binding occurred with all three nuclear fractions, it was preferential for nonhistone proteins. Although there is more evidence to support the interaction of metabolites with DNA in the carcinogenic process, interaction with proteins concerned with the regulation of gene expression may be of significance. (22 refs)

- 79-6831 Effects of Asbestos, Iron Oxide, Silica, and Carbon Black on the Microsomal Availability of

Benzo[a]pyrene. (Eng) Lakowicz, J. R. (Dept. Biochemistry, Univ. Minnesota, Navarre, MN 55392); Bevan, D. R. *Biochemistry* 18(23): 5170-5176; 1979.

Adsorption of the carcinogen benzo(a)pyrene (BP) to iron oxide, silica, and asbestos (anthophyllite and Canadian chrysotile) was found by fluorescence spectroscopy to increase BP uptake in rat liver microsomes, compared with uptake from aqueous dispersions of BP microcrystals. Asbestos particles were more effective than silica and iron oxide in enhancing microsomal uptake of BP. Except for chrysotile, the particles did not disrupt microsomal integrity. Binding of the microsomes to the particles did not affect BP uptake rates. Uptake rates were also independent of microsome and particle concentrations. Adsorption of BP to the particle surface was necessary for enhanced microsomal uptake. Particles, especially fibrous mineral particulates, may thus be cocarcinogenic as a result of their ability to adsorb polynuclear aromatic hydrocarbons and to transport these carcinogens into cells. (37 refs)

- 79-6832 Inhibitory Effect of the Antioxidant Butylated Hydroxyanisole on the Activation of the Carcinogen Benzo(a)pyrene. (Eng) Piekarski, L. (Medical Acad., 02-097 Warsaw, Poland); Sawicki, J.; Kugaczewska, M.; Potocki, L. J.; Sankowski, A.; Uszynski, H.; Malunowicz, E.; Wojciechowska, M.; Kolodziejska, A.; Fox, C. H. *Neoplasma* 26(2): 139-144; 1979.

To investigate the effects of antioxidants on carcinogen and carcinogen metabolite binding to DNA, cultured mouse embryo cells, human skin, and human lymphocytes were incubated with rat liver microsomes and tritium-labeled benzo(a)pyrene (BP: 8.3-25 Ci/mmol) with and without butylated hydroxyanisole (BHA: 0.2 μ mol/ml medium) for 24-48 hr. The amount of BP metabolites bound to DNA in mouse embryo cells and human skin decreased in the presence of BHA, but there was no effect in human lymphocytes. The effect of BHA on BP-DNA binding was also determined for those metabolites of BP extracted in the organic phase. Diols decreased in skin and lymphocyte cultures in the presence of BHA after 48 hr. In mouse embryo cells, there was an increase in phenol when BHA was present in the medium. It is suggested that the decrease in procarcinogen activation, a direct action on biocarcinogens, and increases in procarcinogen and biocarcinogen detoxification could all occur as an effect of BHA. (21 refs)

- 79-6833 Qualitative Changes in the Biologic Characteristics of Cultured Fetal Rat Keratinizing Epidermal Cells During the Process of Malignant Transformation After Benzo(a)pyrene Treatment. (Eng) Indo, K. (Dept. Pathology, Hyogo Coll. Medicine, 1-1, Mukogawa-cho, Nishinomiya, Hyogo, Japan); Miyaji, H. *J Natl Cancer Inst* 63(4): 1017-1027; 1979.

Qualitative changes in the biologic characteristics of fetal SD rat keratinizing epidermal cells undergoing malignant transformation induced by benzo(a)pyrene (BP: 1 μ g/ml) were studied. BP-treated cells at 30 C remained in the premalignant stages and showed shifts in chromosome structure toward the hypodiploid range and parakeratotic changes in their keratinization processes. However, the cells failed to form colonies, even on a plastic substrate. BP-treated cultures that adapted to 35 C or 37.5 C also remained in the premalignant stages, but they acquired the ability to form colonies on plastic substrates during subcultivation. Some transformed colonies appeared among such colonies. Cells showing atypical

keratinization (columnar, spherical, or single-cell types) formed squamous cell carcinomas following injection into syngeneic hosts. The transformed cells showed shifts in chromosome structure toward the hypotetraploid range and formed colonies on 0.57% agar medium, but they failed to form colonies in 0.33% soft agar medium. The cultured cells were classified into five stages of transformation, stage III appearing to be the key step in the process of malignant transformation. (23 refs)

- 79-6834 Induction of Ouabain-resistant Mutation and Sister Chromatid Exchanges in Chinese Hamster Cells with Chemical Carcinogens Mediated by Human Pulmonary Macrophages. (Eng) Hsu, I. C. (Human Tissue Studies Sec., Lab. Experimental Pathology, NCI, Division Cancer Cause and Prevention, Bethesda, MD 20205); Harris, C. C.; Yamaguchi, M.; Trump, B. F.; Schafer, P. W. *J Clin Invest* 64(5): 1245-1252; 1979.

The ability of pulmonary macrophages (PAM) from 20 individuals to mediate mutations and increases in sister chromatid exchanges (SCE) in Chinese hamster V79 cells was studied. PAM metabolically activated benzo(a)pyrene (BP) and its proximate carcinogenic metabolite, (\pm) trans-7,8-dihydroxy-7,8-dihydroBP (7,8-diol), to ultimate mutagens for V79 cells. Increases in the frequency of ouabain-resistant (OR) mutations and SCEs were found only when the V79 cells were cocultivated with both PAM and the chemical procarcinogens. When metabolically activated by PAM, the mean OR mutation frequency caused by BP was $9/10^6$ survival V79 cells/ 10^6 PAM, and a 10-fold interindividual variation (2-21) was observed. The mean OR mutation frequency caused by 7,8-diol was 64, a range of 14-120 being observed. In the absence of PAM, the OR mutation frequency in V79 cells was <1 mutant/ 10^6 survivors. 7,8-Benzoflavone (BF), an inhibitor of mixed function oxidases, reduced the frequency of BP and 7,8-diol induced OR mutations and SCEs in V79 cells. BF did not influence the frequency of OR mutations caused by (\pm)7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydroBP, an ultimate mutagen of BP and 7,8-diol. The data support the hypothesis that PAM may play a role in the activation of environmental chemical procarcinogens. (27 refs)

- 79-6835 Chromosome Aberrations Induced by Benzo(a)pyrene in a Feeder Cell-mediated Assay. (Eng) Nishi, Y. (Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corp., Hatano, Kanagawa 257, Japan); Mori, M.; Inui, N. *Toxicol Lett* 4(4): 275-280; 1979.

Chromosome aberrations induced by benzo(a)pyrene (Bp) in V79 cells were studied in the presence or absence of feeder cells. In the presence of feeder cells, chromosome aberrations at Bp concentrations of 1.0-20.0 μ g/ml depended on feeder cell density. The highest incidences of chromosome aberrations (aberrant cells) and of aberrant chromosomes per 100 metaphase cells were 24.0% and 38.0%, respectively, and were obtained at 20.0 μ g/ml Bp in the presence of 2.0×10^6 feeder cells/60-mm plastic dish. Chromosome aberrations were not induced in the absence of feeder cells. The incidences of aberrant cells and chromosomes on treatment with Bp in the absence of a feeder layer were 3.0-5.0% and 3.0-6.0%, respectively, while the spontaneous rate was 5.0% for both. (14 refs)

- 79-6836 Analysis of Faeces for Benzo(a)pyrene After Consumption of Charcoal-broiled Beef by Rats and

Humans. (Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Grabowski, W.; Groth, K. *Food Cosmet Toxicol* 17(3): 223-227; 1979.

Fecal excretion of benzo(a)pyrene (BP) and its metabolites was studied in male F-344 rats after the administration of various doses of ^{14}C -labeled BP by gavage, and fecal excretion of unchanged BP was investigated in rats and humans after they consumed charcoal-broiled meat containing BP. In groups of 10 rats that received ^{14}C -labeled BP (0.04, 0.4, 4.0 $\mu\text{mol}/\text{rat}$), 74%-79% of the dose was excreted in the feces within the first 48 hr. The proportion of BP excreted unchanged was 13.0%, 7.8%, and 5.6% for the 0.04, 0.4, and 4.0- μmol doses, respectively. The metabolites identified were 3-hydroxybenzo(a)pyrene (3% of dose); 9-hydroxybenzo(a)pyrene (<1%); benzo(a)pyrene-3,6-dione (3%); benzo(a)pyrene-1,6-dione (6%); 4,5-dihydro-4,5-dihydroxybenzo(a)pyrene (<1%); and 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene (<1%). The concentration of BP in a typical sample of broiled beef was $52.7 \pm 6.8 \mu\text{g}/\text{kg}$. Unchanged BP in the feces of rats fed 0.1 kg of beef containing 5.3 μg of BP was 0.6 μg (11% of the dose). No BP was detected in the feces of the eight men who each consumed 357 g of charcoal-broiled beef (8.6 μg BP/person). The detection limit was 0.05 μg BP/total fecal sample; recovery of internal standard ^{14}C -labeled BP was 65% of the dose. (19 refs)

79-6837 Comparative Metabolism of Benzo(a)pyrene in Rodent Liver and Embryonic Cells in Tissue Culture. (Eng) Selkirk, J. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Wiebel, F. J. *Prog Exp Tumor Res* 24: 61-72; 1979.

High-pressure liquid chromatography was used to separate and compare benzo(a)pyrene activation and detoxification products in rat, mouse, and hamster hepatic microsomes and mouse and hamster embryo cell cultures. Metabolite profiles demonstrated the presence of the same type of derivatives, but marked quantitative variations were observed. Microsomal preparations produced large amounts of noncarcinogenic phenols, while intact cell metabolism favored diol formation. Metabolic diols appear to be reactivated as substrates for further activation to a more proximate carcinogenic species of benzo(a)pyrene. These results caution against extrapolating metabolic results from any single test system to other species or tissues. (31 refs)

79-6838 Alterations in the Nasal Mucosa of Syrian Golden Hamsters Exposed to Cigarette Smoke. (Eng) Basur, P. K. (Dept. Biomedical Sciences, Univ. Guelph, Guelph, Ontario, Canada); Harada, T. *Prog Exp Tumor Res* 24: 283-301; 1979.

Syrian golden hamsters subjected for 4 wk to smoke inhalation from three types of Canadian experimental cigarettes were killed 0, 1, or 2 wk after the last smoke exposure, and the cellular response of the nasal mucosa was examined to compare the effect of these cigarettes on regenerative capacity. The incidence of acute rhinitis was greater in all smoke-exposed groups of animals killed immediately after the last exposure than in controls, and the frequency and severity of inflammation were greater in hamsters exposed to the strongest cigarette (rated on the basis of the smoke components). The inflammatory reaction was observed mainly in the respiratory region of the nasal cavity and was characterized by vacuolar degeneration and desquamation of the epithelium ac-

companied by leukocyte infiltration and increased mucous secretion. Surface morphology of the nasal mucosa of smoke-exposed hamsters was characterized by a decrease in the ciliated cell-lined zones and a widening of the squamous cell-lined zones in the anterior nasal fossa. After a 1- or 2-wk recovery period, the inflammatory changes in the smoke-exposed hamsters decreased to control levels, but the regenerated epithelium was atypical in the group exposed to smoke from the strong cigarette. The persistence of some of the cellular changes and the hyperactivity of the mucosal cells of hamsters exposed to smoke from cigarettes high in total particulate matter suggest that the degree of regenerative response may be dependent upon the extent of damage elicited by the type of cigarettes used. (15 refs)

79-6839 Incubation of 3,4-Benzo(a)pyrene With Serum Fractions: Effect on Tumor Production. (Eng) Stenback, F. (Dept. Pathology, Univ. Oulu, Kajaanintie 52D, SF-90220 Oulu, Finland); Curtis, G.; Rowland, J.; Ryan, W. *J Cancer Res Clin Oncol* 95(2): 109-113; 1979.

The effect of incubating 3,4-benzo(a)pyrene (BP) with mouse or rabbit serum gamma-globulin, or albumin on tumor formation in Swiss mice was investigated. BP (3.5 ml of a 25 mg/ml solution in dimethylsulfoxide) was incubated with 31.5 ml of a saline solution containing either 8 g/liter of serum, 1.16×10^{-4} mole/liter of albumin, or 5.12×10^{-5} mole/liter of gamma-globulin. Mice were injected sc with 1 ml of the incubation mixtures. A high incidence of tumors (80%-100%) was obtained with BP incubated with rabbit serum or gamma-globulin, mouse gamma-globulin, or with saline only; and a lower incidence, with BP incubated with rabbit or mouse albumin, or with mouse serum. The number of tumors developing rapidly increased, reaching a plateau after 10 wk; the tumors appeared as small, solitary, firm nodules, slowly increasing in size. Histological examination showed all the tumors to be sarcomas. These data suggest that binding of BP to serum proteins (particularly albumin) reduces its tumorigenicity. (14 refs)

79-6840 Determination of Benzo(a)pyrene in Smoked, Cooked and Toasted Food Products. (Eng) Lintas, C. (Istituto Nazionale Nutrizione, Rome, 00161, Italy); De Matthaeis, M. C.; Merli, F. *Food Cosmet Toxicol* 17(4): 325-328; 1979.

Benzo(a)pyrene content was analyzed in samples of smoked, cooked, and toasted food products as well as oils and fats commercially available in Italy. Benzo(a)pyrene was detected in approx 73% of the samples, at levels ranging from 0.01 to 9.51 $\mu\text{g}/\text{kg}$. In electrically-broiled foods, the benzo(a)pyrene content ranged from 0 to 0.05 $\mu\text{g}/\text{kg}$. Levels of benzo(a)pyrene found in the food products analyzed were lower than levels reported by other investigators for comparable food commodities. (28 refs)

79-6841 Effect of Dietary Fats on Tumorigenicity of Two Sarcoma Cell Lines. (Eng) Corwin, L. M. (Dept. Microbiology, Cancer Res. Center, Boston Univ. Sch. Medicine, Boston, MA 02118); Varshavsky-Rose, F.; Broitman, S. A. *Cancer Res* 39(11): 4350-4355; 1979.

Continuous in vitro passage in lipid-depleted media of a Kirsten sarcoma virus-transformed murine cell line (FK3T3) led to the establishment of AK3T3, a new cell line exhibiting many of the in vitro growth characteristics of the untransformed parent cell line,

BALB/3T3, A31 strain. The tumorigenicity of the AK3T3 cell line was compared with FK3T3 cells in mice fed diets varying in levels of polyunsaturated fatty acids (PUFA). Tumorigenicity of FK3T3 cells increased as the PUFA level decreased. On the other hand, tumorigenicity of AK3T3 cells decreased as dietary PUFA levels decreased. Fatty acid composition and membrane microviscosities did not differ from those of the BALB/3T3 parent strain. A correlation between tumorigenicity and cholesterol content was observed. The cholesterol levels of the FK3T3 strain were not influenced by cholesterol levels in the medium, whereas the AK3T3 and the parent BALB/3T3 cells were markedly altered, both strains having low levels when grown in delipidized media. Thus, when grown in vivo in mice fed a diet very low in PUFA and cholesterol, AK3T3 cells had lowered tumorigenicity, whereas FK3T3 cells, which can maintain their cholesterol levels under these conditions, were quite tumorigenic. AK3T3 cells were less able than FK3T3 cells to produce an immune response in vivo and to respond to specific cell-mediated cytotoxicity. It is suggested that the use of these mostly isogenic tumor strains may offer a good model system of the specific cellular alteration which affects the responses of different tumors to dietary PUFA. (24 refs)

- 79-6842 Inhibition of 2-Fluorenamine-induced Mutagenesis in *Salmonella typhimurium* by Vitamin A. (Eng) Baird, M. B. (Masonic Medical Res. Lab., Utica, NY 13503); Birnbaum, L. S. *J Natl Cancer Inst* 63(4): 1093-1096; 1979.

Retinol completely inhibited the mutagenicity of the carcinogen 2-fluorenamine (2-FA) in *Salmonella typhimurium* TA98 when the mutagen was activated by liver microsomes from CFN rats. The mutagenicity of 2-FA activated by the 9,000 x g rat liver supernatant S9 was inhibited by retinol to a lesser degree. The decline in the number of his revertants was not an artifact due to bacterial killing, inasmuch as retinol was not toxic to the bacteria at levels that totally inhibited mutagenesis by 2-FA. Mutagenesis induced by adriamycin, which does not require metabolic activation for its mutagenic potential, was unaffected by vitamin A. These results indicate that retinoids inhibit the metabolic activation of some chemical carcinogens to forms that can interact with DNA. The findings are consistent with the hypothesis that retinoids exert anticancer activity by inhibiting carcinogen activation, thereby inhibiting tumor induction, in addition to their more widely accepted role in modulating the proliferation of neoplasms derived from epithelium. (24 refs)

- 79-6843 Retinol Inhibition of Ornithine Decarboxylase Induction and G₁ Progression in Chinese Hamster Ovary Cells. (Eng) Haddox, M. K. (Dept. Pharmacology, Univ. Arizona Health Sciences Center, Tucson, AZ 85724); Scott, K. F.; Russell, D. H. *Cancer Res* 39(12): 4930-4939; 1979.

Vitamin A inhibition of ornithine decarboxylase (ODC) induction was studied in the G₁ phase of the cell cycle of synchronous Chinese hamster ovary (CHO) cell cultures. The retinol-promoted inhibition of ODC was not the result of an effect on general protein synthesis, was effective only in G₁ prior to the time an increase in ODC activity had begun, did not involve disruption of the G₁-phase increase in cyclic adenosine 3':5'-monophosphate-dependent protein kinase activity, and required transcription-dependent events for reversal. The inhibition of ODC induction was associated with a block of cell cycle progression in the G₁ phase. There was no incorporation of [³H]thymidine in the presence of the vitamin, nor was induction of S-phase-dependent

S-adenosyl-L-methionine decarboxylase or ultimate cell doubling observed. The inhibition of ODC and the inhibition of S-phase transition displayed a similar concentration dependence, with 60% inhibition occurring in the presence of 80 μ M retinol; they were also similar in their dependence on cell locus in early G₁ phase for efficacy and in a reversal after removal of the vitamin, with the increase in ODC preceding the increase in S-phase transition in a parallel fashion. Arrest of the cells at the G₁ retinol-sensitive restriction point prior to ODC induction resulted in the inhibition of the G₁-phase-dependent increase in RNA synthesis. Other naturally occurring retinoids also inhibited CHO cell growth (retinal > retinol > retinyl acetate > retinoic acid). Retinal, the most potent, displayed a paradoxical effect on CHO cells: it stimulated CHO growth parameters and ODC activity at very low concentrations (1 to 5 μ M), but at high concentrations, inhibited in a manner similar to that described for retinol. (74 refs)

- 79-6844 A Possible Naturally Occurring Tumor Promoter, Teleocidin B from *Streptomyces*. (Eng) Fujiki, H. (Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan); Mori, M.; Nakayasu, M.; Terada, M.; Sugimura, T. *Biochem Biophys Res Commun* 90(3): 976-983; 1979.

Dihydrateleocidin B, a derivative of teleocidin B, caused marked induction of ornithine decarboxylase within 4 hr of painting on mouse skin. Induction was maximal at doses of from 5 to 7.5 μ g. Painting the skin with 13-cis-retinoic acid one hr prior to dihydrateleocidin B application inhibited this enzyme induction. Dihydrateleocidin B induced cell adhesion of human promyelocytic leukemia cells (HL-60) to the surface of culture flasks and inhibited terminal differentiation of Friend erythroleukemia cells induced by dimethyl sulfoxide. Its effective dose for these actions as compared to the potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was about one fifth of that required for TPA. Teleocidin B appears to be a new type of tumor promoter. (18 refs)

- 79-6845 Influence of Vitamin A on the Laryngeal Response of Hamsters Exposed to Cigarette Smoke. (Eng) Meade, P. D. (Biomedical Sciences, Ontario Veterinary Coll., Univ. Guelph, Guelph, Ontario N1G 2W1, Canada); Yamashiro, S.; Harada, T.; Basrur, P. K. *Prog Exp Tumor Res* 24: 320-329; 1979.

The effects of vitamin A (given as a 15,000 or 25,000 IU retinyl palmitate supplement) on the latency to onset of histopathological changes in the larynx were studied in male Syrian golden hamsters exposed to long-term smoke inhalation (smoke from 8 cigarettes/day for 6 wk). The histopathological changes in the smoke-exposed hamsters supplemented with vitamin A did not differ significantly from those in the unsupplemented smoke-exposed hamsters. Liver and plasma vitamin A levels were higher in supplemented than in unsupplemented animals and were significantly lower in smoke-exposed than in sham-exposed hamsters. In hamsters maintained for 14-28 wk on a vitamin A-free diet, a moderate degree of squamous metaplasia of the surface and glandular epithelium of the larynx was noted. Similarly, the incidence of metaplasia of the laryngeal and glandular epithelium was higher in smoke-exposed hamsters maintained for 100 days on vitamin A-free diets than in smoke-exposed animals maintained on normal diets. The frequency of such histopathological changes was highest near the area of transition from stratified squamous to ciliated pseudostratified columnar epithelium. The data support the

hypothesis that animals exposed to cigarette smoke and fed a vitamin A-free diet are at higher risk of developing tumors than smoke-exposed animals given adequate vitamin A. (23 refs)

- 79-6846 Transplacental Effects of Diethylstilbestrol in Mice. (Eng) McLachlan, J. A. (Environmental Toxicology Branch, US Dept. Health, Education and Welfare, Research Triangle Park, NC 27709). *Natl Cancer Inst Monogr* (51): 67-72; 1979.

The placental transfer of (³H)- or (¹⁴C)-labeled diethylstilbestrol (DES) was studied in CD-1 mice together with the effects of prenatal DES exposure on postnatal development of genital tract function in male and female offspring. Pregnant mice received 0.01-100 µg/kg DES iv or sc on gestation days 9-16. DES-associated radioactivity in the fetal plasma approximated maternal plasma 1/2 hr after iv administration of (³H)DES; (³H)-activity associated with DES in the fetal genital tract was about threefold higher. The decrease in reproductive capacity of female offspring from mice treated with DES during gestation was dose related; a low incidence (10% or less) of cancer of the vagina, cervix, and/or uterus was also observed in these mice. Male offspring exposed prenatally to the highest dose (100 µg/kg) of DES also had lower reproductive capacities. Genital tract lesions in these mice included epididymal cysts, inflammation, cryptorchidism, and nodular masses in the seminal vesicles and/or prostate gland. Such lesions and sterility were not observed at the lower DES doses. Histologic studies suggested that müllerian duct tissue may represent a site for the transplacental toxicity of DES in both the male and female fetus. (28 refs)

- 79-6847 Synergism of Diethylstilbestrol and Radiation in Mammary Carcinogenesis in Female F344 Rats. (Eng) Holtzman, S. (Medical Dept., Brookhaven Natl. Lab., Upton, NY 11973); Stone, J. P.; Shellabarger, C. J. *J Natl Cancer Inst* 63(4): 1071-1074; 1979.

The possibility that diethylstilbestrol (DES) and radiation could act synergistically in the production of mammary tumors was investigated. One 20-mg pellet containing cholesterol only or cholesterol mixed with 0.98, 1.6, 2.6, or 3.9 mg of DES was implanted sc in each of 203 female F344 rats. Two days later, half the animals in each group were exposed to 150 R of x-rays, and the remaining animals were sham-irradiated. During the 350-day observation period, mortality was higher in groups given the higher doses of DES, with or without x-rays. Pituitary tumors and pyometritis were seen in rats given any DES dose, with or without x-ray treatment. Only rats that received both DES and x-rays developed mammary adenocarcinomas (AC). A synergistic AC response occurred in the group that received 2.6 mg DES plus x-rays; synergism was defined as a significantly greater incidence of rats with mammary tumors resulting from DES plus x-ray treatment when compared with the summed incidence from comparable individual treatments. For all other groups that received both treatments, synergism was detected only when their data were combined. Synergism was not detected among rats that had fibroadenomas (FA). Both types of neoplasms were independent phenomena, as no significant relationship was found between the incidences of FA and AC. (17 refs)

- 79-6848 Identification of Some Products from the Reaction of *Trans*-4-Aminostilbene Metabolites and Nucleic Acids

In Vivo. (Eng) Gaugler, B. J. (Institut für Pharmakologie und Toxikologie der Universität Würzburg, Versbacher Strasse 9, 8700 Würzburg, W. Germany); Neumann, H. G.; Scribner, N. K.; Scribner, J. D. *Chem Biol Interact* 27(2/3): 335-342; 1979.

Highly and specifically labeled [³H]*trans*-4-dimethylaminostilbene was prepared and administered to female Wistar rats, and the liver RNA was isolated and hydrolyzed. The hydrolysate was chromatographed and a series of nucleoside adducts was obtained. Identification between labeled in vivo and unlabeled in vitro adducts was accomplished. 1-(4-Acetamidophenyl)-1-(3-uridylyl)-2-hydroxy-2-phenylethane, 1-(4-acetamidophenyl)-1-(1-guanosyl)-2-hydroxy-2-phenylethane, 3-(β-D-ribose)-7-phenyl-8-(4-acetamidophenyl)-7,8-dihydroimidazo-[2,1-i]-purine, and a guanosyl-O⁶ derivative were formed in vivo when the carcinogen *trans*-4-dimethylaminostilbene was administered po to the female rats. Upon hydrolysis, rat-liver RNA released 1-(4-acetamidophenyl)-2-phenyl-1,2-ethanediol. Comparison of the adduct patterns resulting from the reaction of N-acetoxy-N-acetylaminostilbene with yeast RNA in vitro with those obtained from the same reaction with in vitro rat liver RNA revealed both quantitative and qualitative differences. This indicated that reactive metabolites other than hydroxamic acid esters may have contributed to the in vivo binding. (10 refs)

- 79-6849 The Effects of Sex Hormones on the Development of Urinary Bladder Tumors Induced by N-Butyl-N-(4-Hydroxybutyl) Nitrosamine in Rats. (Jpn) Iriya, K. (Dept. Urology, Nara Medical Univ., Kashiwara City, Nara Pref. 634, Japan). *Nara Igaku Zasshi* 30(1/2): 69-82; 1979.

The effects of diethylstilbestrol and testosterone on the development and growth of N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)-induced urinary bladder tumors in 129 male and 120 female 10-wk-old Wistar rats were studied. Rats received 0.05% BBN po in drinking water for 6 wk followed by a BBN-free diet for 18 wk and then sacrificed. Before (1 wk) or after BBN administration, orchiectomized or intact male rats received 50-mg diethylstilbestrol sc pellet implants; ovariectomized or intact females received 50-mg testosterone sc pellet implants. Bladder tumors developed in 6/10 male and 2/11 female control rats. In male rats given BBN 1 wk after implantation of diethylstilbestrol alone or those that received diethylstilbestrol and underwent orchiectomy, the incidence of tumors was 1/14 and 0/12 respectively, while tumors occurred in 5/12 rats that underwent orchiectomy alone. The incidence of tumors in male rats given diethylstilbestrol implants (without or with orchiectomy) after 6 wk of BBN was 1/17 and 1/12, and that in rats given orchiectomy alone after BBN treatment was 4/11. The incidence of tumors in female rats given testosterone, testosterone plus ovariectomy, or ovariectomy 1 wk before BBN administration was 4/11, 5/10, and 4/11, respectively, and the incidences in rats given testosterone alone, testosterone plus ovariectomy, or ovariectomy alone were 6/11, 8/11, and 6/11. The results indicate that orchiectomy had no influence on inhibition of carcinogenesis, that diethylstilbestrol inhibited carcinogenesis and the growth of tumors in male rats, that testosterone promoted the growth of bladder tumors in female rats, and that there was a higher incidence of BBN-induced urinary bladder tumors in male than in female rats. (33 refs)

- 79-6850 Effects of Transplacental Exposure to Diethylstilbestrol on Carcinogenic Susceptibility During Postnatal Life in Hamster Progeny. (Eng) Rustia, M. (Eppley Inst.

Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE 68105); Shubik, P. *Cancer Res* 39(11): 4636-4644; 1979.

Prenatal exposure to a single dose of diethylstilbestrol (DES) produced a significant increase in carcinogenic response of hamster progeny that were subsequently subjected to the carcinogenic stimulus of 7,12-dimethylbenz(a)anthracene (DMBA) during postnatal life. Pregnant Syrian golden hamsters received a single dose of DES, 10 mg/kg, on day 14 of gestation. Postnatally, at 6 wk of age, the progeny were given DMBA, 25 mg/kg po twice/wk for 8 wk. The second group (not exposed in utero to DES) received DMBA at 6 wk of age, 30 mg/kg po, twice/wk for 18 wk. The progeny exposed to DES prenatally and DMBA postnatally developed a greater multiplicity of tumors per tumor-bearing animal ($p < 0.001$) and higher rates of neoplasms of the reproductive tract (ovarian and uterine), mammary gland, and forestomach, as well as of dermal melanomas. The prenatally DES-exposed progeny also had significantly higher incidences of malignant tumors, eg carcinomas of the mammary gland ($p < 0.001$) and carcinomas of the forestomach ($p < 0.001$), than did the hamsters given DMBA alone. Endocrine imbalance produced by exposure in utero may heighten the sensitivity of the progeny to development of neoplasms after a challenge with carcinogenic stimuli in adult life. The relevance of these experimental data to the human situation is discussed. (47 refs)

79-6851 Diethylstilbestrol: Evidence for Metabolic Activation in Man, Rat, and Hamster. (Eng) Metzler, M. (Institut für Pharmakologie und Toxikologie, Universität Würzburg, Versbacher Landstrasse 9, W. Germany). *Natl Cancer Inst Monogr* (51): 73-76; 1979.

Male and female Wistar rats (200-250 g), male Syrian golden hamsters (150-200 g), and two male human volunteers (aged 41 and 32 yr) were given radioactive diethylstilbestrol (DES) and metabolites extracted from urine and bile were analyzed. Urinary and biliary radioactivity was predominantly (60%-80%) associated with glucuronides. Two of the major biliary metabolites for rats and hamsters were mono- and dimethoxy-DES. The two methoxy groups in dimethoxy-DES were attached to different aromatic rings. Dienestrol was present in both bile and urine from these animals. The major urinary DES metabolites in rats and hamsters were ω -hydroxy-DES, methoxydienestrol, and ω -hydroxydienestrol. A cleavage product of DES, migrating with 4'-hydroxypropeophenone in chromatographic separation, represented a major urinary metabolite in male rats. In the human males, glucuronides, comprising 80%-90% of the urinary radioactivity, contained DES, dienestrol, and ω -hydroxydienestrol. Fecal material contained about 30% of the dose; almost all was unconjugated material. Only DES could be identified in fecal extracts. The 24-hr urine of a woman breast cancer patient treated with unlabeled DES showed DES, dienestrol, and hydroxydienestrol. Thus, at least seven DES metabolites are formed in vivo, some of which are potentially reactive. (23 refs)

79-6852 Developmental Mechanism of Estrogen-induced Irreversible Changes in the Mouse Cervicovaginal Epithelium. (Eng) Forsberg, J. G. (Inst. Anatomy, Univ. Bergen, Arstadveien 19, 5000 Bergen, Norway). *Natl Cancer Inst Monogr* (51): 41-56; 1979.

Neonatal female NMRI mice were inoculated sc with 5 μ g/day of 17 β -estradiol or diethylstilbestrol (DES) and were studied with

respect to the immediate and long-term effects of estrogen exposure on the cervicovaginal epithelium. The estrogens inhibited proliferation of the pseudostratified columnar epithelium in the upper part of the müllerian vagina. This resulted in the occurrence of regions containing a columnar epithelium (CE) in the uterine cervix and upper vagina of adult animals instead of the normal squamous epithelium. Later, the CE developed into adenosis; subsequently, suspected malignant changes were seen. In addition to these morphologic changes, neonatal estrogen treatment resulted in changes in the amount of cervicovaginal antigenic (CVA) material. Compared with control levels, CVA titers were high in the superficial mucified vaginal cells of neonatally DES-treated mice that were subsequently castrated and given estrogen as adults. The CE had a low level of CVA. An interaction between estradiol and prolactin was important for the CVA level; neonatal estrogen treatment may result in persistent changes in the regulation of plasma prolactin. A comparison is made between the estrogen-induced changes in mice and the effects of DES in the female offspring of women exposed to DES during pregnancy. The importance of the mouse model for the study of the estrogen-induced changes and other factors influencing the development of human clear cell adenocarcinomas of the vagina and cervix is stressed. (78 refs)

79-6853 Development of Permanently Proliferated and Cornified Vaginal Epithelium in Mice Treated Neonatally with Steroid Hormones and the Implication in Tumorigenesis. (Eng) Takasugi, N. (Dept. Biology, Faculty Science, Okayama Univ., Tsushima, Okayama 700, Japan). *Natl Cancer Inst Monogr* (51): 57-66; 1979.

Five to ten daily injections of 5-20 μ g 17 β -estradiol, 20-100 μ g testosterone and its propionate, and 100 μ g 5 α -dihydrotestosterone, starting within 24 hr of birth, caused persistent proliferation and cornification of the vaginal epithelium in female C57BL/Tw, C57BL/Ms, A/Ms, and A/Crgl mice. The cornification was independent of endogenous estrogen, and hyperplastic lesions were frequent in the altered vaginal epithelium. In C57BL/Tw mice, some undifferentiated cells, which survive only a few days postnatally in normal animals, appeared to transform into large cells and formed nodules after neonatal administration of 17 β -estradiol. The primary normal epithelium was replaced by a sheet of fused nodules that showed persistent proliferation and cornification independent of estrogen. The occurrence of the estrogen-independent vaginal cornification in C57BL mice receiving neonatal injections of 20 μ g estradiol for 5 days was prevented by injections of vitamin A acetate (200 IU) when given simultaneously with the estradiol. Light cells (ie, cells with reduced cytoplasmic electron density) were found by electron microscopy in the epithelium of mice treated with estradiol + vitamin. These cells may be significant in degeneration of permanently changed vaginal epithelium. (39 refs)

79-6854 The Occurrence of Adenocarcinoma in Endometriosis of the Rectovaginal Septum During Progestational Therapy. (Eng) Addison, W. A. (Dept. Obstetrics and Gynecology, Duke Univ. Medical Center, Box 3296, Durham, NC 27710); Hammond, C. B.; Parker, R. T. *Gynecol Oncol* 8(2): 193-197; 1979.

The case report of a patient who developed adenocarcinoma in endometriosis of the rectovaginal septum during a second course of hormonal therapy is presented. The patient presented at the age of

37 with rectal and vaginal bleeding due to endometriosis. Pelvic examination revealed a mobile, rubbery mass approx 5 x 5 x 6 cm occupying the rectovaginal septum. The symptoms resolved promptly upon induction of pseudopregnancy with Enovid (20 mg/day). This was discontinued after 9 mo due to weight gain, fluid retention, and elevated blood pressure. The symptoms returned after 6 mo and the patient was treated with im Depo-Provera (200 mg/wk x 4, followed by 200 mg/mo). There was an initial response, but after 3 mo of therapy, the mass was significantly enlarged. A biopsy taken from the same area as previous biopsies showing endometriosis now showed adenocarcinoma. The patient died of abdominal carcinomatosis, despite chemotherapy. Twelve cases of primary adenocarcinoma arising in areas of endometriosis in the rectovaginal septum have been reported. Malignant transformation in an area of endometriosis during sex steroid therapy has not been reported previously. (8 refs)

- 79-6855 The Histology of Liver Tumors in Oral Contraceptive Users Observed During A National Survey by the American College of Surgeons Commission on Cancer. (Eng) Nime, F. (Dept. Pathology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Pickren, J. W.; Vana, J.; Aronoff, B. L.; Baker, H. W.; Murphy, G. P. *Cancer* 44(4): 1481-1489; 1979.

As part of the national survey on the tumorigenesis of oral contraceptives conducted by the American College of Surgeons' Commission on Cancer, 94 cases of liver tumors in oral contraceptive users and non-users were studied histologically. Pathologic criteria were established prior to studying the slides; the results were then tabulated to determine the significance of each of the criteria as related to the use of contraceptives. These criteria included tumor size and the presence or degree of peliosis hepatis, hemorrhage, necrosis, fibrosis, thrombosis, or vascular alterations of the intima and media. Livers showing focal nodular hyperplasia in pill users exhibited greater vascular alterations, fibrosis, peliosis, and tumor size compared with livers showing focal nodular hyperplasia from non-pill users. Hemorrhage, necrosis, and peliosis were much more common in liver cell adenoma than in focal nodular hyperplasia. In the material reported in this series, there were no cases of liver cell adenoma among non-pill users. The livers showing focal nodular hyperplasia exhibited an overwhelmingly greater degree of vascular intimal and medial alterations than did those showing liver cell adenoma. The results suggest that oral contraceptives primarily affect the liver vasculature. (19 refs)

- 79-6856 Sister-Chromatid Exchanges in Oral Contraceptive Users. (Eng) Murthy, P. B. (Natl. Inst. Nutrition, Indian Council Medical Res., Jamai Osmania P.O., Hyderabad-500 007, India); Prema, K. *Mutat Res* 68(2): 149-152; 1979.

The frequencies of sister-chromatid exchanges (SCE) in the peripheral lymphocytes of 15 nonpregnant women, 15 women in the third trimester of pregnancy, and 15 women who had been taking oral contraceptives (OC, 150 µg *d*-norgestrel and 30 or 50 µg ethinyl estradiol/day) for 6-24 mo (mean 16 mo) were determined. The women ranged in age from 18 to 35 yr (mean 23.6 yr). The mean number of SCE/cell was significantly higher in the OC users (9.7) than in the pregnant controls (5.8) and nonpregnant controls (6.3). This increase was observed in most OC users. The results indicate the existence of an increased mutagenic environment in the peripheral lymphocytes of OC users; this environment is caused by either the OC itself or by a metabolite(s). (12 refs)

- 79-6857 Effects of Progesterone and R2323 on the Development of Dimethylbenzanthracene-induced Mammary Tumors. (Eng) Kelly, P. A. (Medical Res. Council Group in Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Quebec G1V 4G2, Canada); Asselin, J.; Turcot-Lemay, L.; Labrie, F.; Raynaud, J. P. *Eur J Cancer* 15(10): 1243-1251; 1979.

Progesterone (PRG: 0.5 or 4.0 mg/day, sc) or the antiprogesterin 13 α -ethyl-17-hydroxy-18, 19-dinor-17 β -pregna-4, 9, 11-triene-20-yn-3-one (R2323: 2.5-150 µg/day, sc) was given to female Sprague-Dawley rats (50-55 days old), beginning the day after iv injection of 7,12-dimethylbenz(a)anthracene (DMBA: 5 mg/rat). Mammary tumor development was followed for 133-141 days after DMBA treatment. Both doses of PRG promoted early mammary tumor growth, although the max tumor prevalence and the max number of tumors/rat (measured on day 141) were similar to control values. At the lower PRG dose, the tumors were much larger than those in vehicle-treated controls, and tumor estradiol (E2) binding was increased slightly. The higher PRG dose reduced tumor binding of R5020 (17,21-dimethyl-19-nor-pregna-4, 9-diene-3-dione). Both doses of PRG caused a significant reduction in plasma luteinizing hormone (LH) levels, but they did not affect plasma prolactin (PRL) levels or tumor PRL binding. R2323 caused a dose-related inhibition of tumor development and a marked reduction in plasma LH, but it had no significant effect on plasma PRL levels or tumor levels of E2, PRG, or PRL receptors (compared with control tumors). This inhibition of gonadotropin secretion might be mainly responsible for the marked antitumor activity of R2323, although part of the inhibitory effect might be exerted directly at the tumor level. (32 refs)

- 79-6858 Effect of Pituitary Isografts on the Concentration of Estrogen and Glucocorticoid Receptors in C3H Mice Mammary Tumors. (Eng) Coezy, E. (Unité 148 de l'Inserm, 60, rue de Navacelles, 34100 Montpellier, France); Rochefort, H. *Eur J Cancer* 15(10): 1185-1189; 1979.

The effects of pituitary isografts on the induction and steroid receptor levels of mammary tumors were investigated in C3H mice. The latent period of tumorigenesis was shortened, but the final tumor incidence was unaffected. Pituitary grafting resulted in a threefold increase in the concentration of cytosol estrogen receptor sites in the tumors when measured 1 day after ovariectomy; however, the affinity of the receptor for estradiol was not modified. In contrast, glucocorticoid receptor levels were not increased, and the progesterone receptor concentration was negligible with or without pituitary grafts. The sustained high prolactin levels in the mice grafted with pituitaries are probably responsible for the increase in the estrogen receptor site concentration. The authors propose that the stimulating effect of prolactin on mammary tumor induction might not only be due to the activation of prolactin receptors but also to the accumulation of the estrogen receptor, resulting in local hypersensitivity to estrogens. (19 refs)

- 79-6859 Formation and Removal of Aflatoxin B₁-induced DNA Lesions in Epithelioid Human Lung Cells. (Eng) Wang, T. V. (Dept. Carcinogenesis, Swiss Inst. for Experimental Cancer Res., CH-1066 Epalinges-Lausanne, Switzerland); Cerutti, P. A. *Cancer Res* 39(12): 5165-5170; 1979.

The formation and removal of covalent aflatoxin B₁ (AFB)₁:DNA adducts under nontoxic conditions were studied in metabolically active epithelioid human lung cells (A549). After 24 hr exposure to

0.82 μM AFB₁, the adduct level was in the range of 0.16 to 1.34 $\mu\text{moles adduct/mole DNA-phosphate}$. Approx 60% of the total initial AFB₁ adducts were removed rapidly during the first 24 hr of posttreatment incubation of A549 cells, while only 15% of the total adducts were released from free AFB₁:DNA isolated from A549 cells within the same time period under physiological conditions *in vitro*. The remaining 40% of the adducts were removed very slowly, leaving a sizable fraction of residual lesions in the DNA over several generation times. Of three products distinguishable by Sephadex LH 20 and high-pressure liquid chromatography in formic acid hydrolysates of DNA from A549 cells immediately following AFB₁ treatment, 2,3-dihydro-2-(N'-guanyl)-3-hydroxyafatoxin B₁ was predominant (42%-64%). The disappearance of lesions assayed as this product in acid hydrolysates of DNA was rapid and occurred with similar kinetics upon incubation of intact cells in culture or of free DNA *in vitro* under physiological conditions. For free AFB₁:DNA, the disappearance of these lesions is in part due to their transformation to more stable secondary derivatives which remain attached to the DNA backbone. As with the *in vitro* situation, it is likely that a portion of the primary lesions in A549 cells are also first modified either spontaneously or enzymatically to secondary lesions which are then processed by the cellular repair pathways. (18 refs)

79-6860 Promotion of Azoxymethane-induced Intestinal Cancer by High-Fat Diet in Rats. (Eng) Bull, A. W. (Dept. Surgery, Wayne State Univ. Sch. Medicine, Detroit, MI 48201); Soullier, B. K.; Wilson, P. S.; Tan Hayden, M. T.; Nigro, N. D. *Cancer Res* 39(12): 4956-4959; 1979.

Promotion of intestinal cancer by a high-fat diet was studied by feeding a 30% beef diet to 8 groups of rats (25 rats/group) for time periods varying from 1 to 21 wk after 8 weekly sc injections of azoxymethane (AOM, 8 mg/kg). Two other groups were fed the high-fat diet, one for 8 wk prior to and the other during AOM injections. A 5% fat diet was fed to rats when not on the 30% fat diet and to a control group of 25 animals. The high-fat diet increased intestinal tumor frequency as much as twofold when given for at least 4 wk after but not during or prior to AOM injections; this increase occurred even after a prolonged interval (10 wk) between the last AOM injection and the high-fat diet. In general, tumor frequency increased according to the length of time animals were fed the high-fat diet after AOM. The high-fat diet in this model exhibited most of the properties of promoters of murine skin cancer. These results support the concept that excess dietary fat acts at the promotional phase of carcinogenesis. (15 refs)

79-6861 Tumorigenicity of Bay-Region Epoxides and Other Derivatives of Chrysene and Phenanthrene in Newborn Mice. (Eng) Buening, M. K. (Dept. Biochemistry, Hoffmann-La Roche, Inc., Nutley, NJ 07110); Levin, W.; Karle, J. M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 39(12): 5063-5068; 1979.

The tumorigenic activity of the bay-region diol-epoxides and tetrahydroepoxides of chrysene and phenanthrene was tested in newborn Swiss-Webster mice. The test compounds were given on the 1st, 8th, and 15th days of life (0.2, 0.4, and 0.8 $\mu\text{mol ip}$, respectively) and the animals were observed until they were 38-42 wk old. (\pm)-1 β ,2 α -Dihydroxy-3 α ,4 α -epoxy-1,2,3,4-tetrahydrochrysene, in which the epoxide is *trans* to the benzylic 1-hydroxyl group was the most tumorigenic chrysene derivative tested, producing pulmonary

tumors in 98% of the mice, with an av of 15.9 tumors/mouse. (\pm)-1 β ,2 α -Dihydroxy-3 β ,4 β -epoxy-1,2,3,4-tetrahydrochrysene, in which the bay region epoxide oxygen is *cis* to the benzylic 1-hydroxyl group, had little tumorigenic activity. *trans*-2-Dihydroxy-1,2-dihydrochrysene and 1,2-dihydrochrysene and 1,2-dihydrochrysene, the immediate metabolic precursors of a bay-region diol-epoxide and a bay-region tetrahydroepoxide, respectively, were the next most active chrysene derivatives tested. They produced pulmonary tumors in 73%-75% of the mice, with an av of 2.1-2.2 tumors/mouse. 3,4-Epoxy-1,2,3,4-tetrahydrochrysene (bay-region epoxide) induced pulmonary tumors in 71% of the mice, with an av of 1.26 tumors/mouse. Other chrysene derivatives tested had little or no tumorigenic activity. Chrysene had little tumorigenic activity in the lung but induced liver tumors in 25% of the mice. The bay-region tetrahydroepoxide, 3,4-epoxy-1,2,3,4-tetrahydrophenanthrene, induced pulmonary tumors in 45% of the mice, with an av of 0.74 tumors/mouse. Phenanthrene and its other derivatives tested had little tumorigenic activity. It is concluded that the carcinogenicity of chrysene follows the predictions of the bay-region theory. The small size and resulting increased polarity of the phenanthrene diol-epoxides and tetrahydroepoxides may limit their intrinsic activity. (25 refs)

79-6862 Formation and Subsequent Excision of O⁶-Ethylguanine from DNA of Rat Liver Following Administration of Diethylnitrosamine. (Eng) Pegg, A. E. (Dept. Physiology, Milton S. Hershey Medical Center, Hershey, PA 17033); Balog, B. *Cancer Res* 39(12): 5003-5009; 1979.

The alkylation of rat liver DNA was studied at short times after ip injection of low (0.5-4 mg/kg) and high (10-100 mg/kg) doses of diethylnitrosamine (DEN). Ethylation of DNA, measured by the production of 7-ethylguanine, was almost complete within 30 min after the 0.5-mg/kg dose of DEN, within 90 min after 2 mg/kg, and within 120 min after 4 mg/kg. O⁶-ethylguanine levels decreased by 33% between 30 and 120 min after the injection of 0.5 mg/kg DEN. A loss of O⁶-ethylguanine also occurred from liver DNA shortly after 2- and 4-mg/kg doses of DEN. A ratio of O⁶-ethylguanine:7-ethylguanine in the ethylated DNA close to 0.71 (the value found by reaction of DNA *in vitro* with N-ethyl-N-nitrosourea) was found only at the earliest times measured or only after doses ≥ 10 mg/kg. This suggests that the higher O⁶-ethylguanine:7-ethylguanine ratio observed at higher DEN exposures is due to rapid excision of O⁶-ethylguanine from the DNA. The half-life of O⁶-ethylguanine and O⁶-methylguanine from 1.4-0.1 $\mu\text{mol/mol guanine}$ was 1.5-3 hr and the max rate of removal was 1.5 $\mu\text{mol/mol guanine/hr}$. Comparisons of losses in the range 14-8 $\mu\text{mol/mol guanine}$ showed half-lives of 6-8 hr and removal rates of 1.5 $\mu\text{mol/mol guanine/hr}$. A cell-free extract that specifically catalyzed the removal of O⁶-ethylguanine from DNA was isolated from rat liver. The same preparation produced approx equal rates of O⁶-methylguanine removal from methylated DNA and O⁶-ethylguanine removal from ethylated DNA when the substrate concentrations were similar. The rapid repair observed in these studies may be important in limiting the potential for neoplastic change after exposure to low dietary levels of these carcinogens. (36 refs)

79-6863 Effect of Age at Treatment on Incidence and Type of Renal Neoplasm Induced in the Rat by a Single Dose of Dimethylnitrosamine. (Eng) Hard, G. C. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140). *Cancer Res* 39(12): 4965-4970; 1979.

Groups of Porton albino Wistar rats received a single ip injection (30 mg/kg body wt) of dimethylnitrosamine at 24 hr; at 3 wk; and at 1, 1.5, 2, 3, 4, and 5 mo of age. In all groups except the neonates, the animals were preconditioned by feeding a no-protein, high-carbohydrate diet for 5 days prior to carcinogen injection. In the neonatal group, the dose of carcinogen had to be reduced to 20 mg/kg in order to achieve approx equivalent numbers of survivors. Notwithstanding the loss of strict comparability of data between the newborns and the remaining age groups, kidney tumor incidence showed a bimodal distribution represented by the occurrence of two separate entities, renal mesenchymal tumor and cortical epithelial tumor. Mesenchymal tumor proved to be a neoplasm of the neonatal and immature rat; susceptibility to this tumor fell rapidly after 1 mo of age to nil at 5 mo of age. Susceptibility to tumors of cortical tubule epithelium increased with ensuing sexual maturity but declined by 5 mo of age. Age at dosing also influenced to some degree the grade of tumor induced. An altered grade of mesenchymal tumor was illustrated by the emergence in older age groups of a fibroma-like variant not encountered in earlier groups while epithelial tumors graded as carcinomas were not induced in rats dosed at 5 mo of age. The adenomas in the latter group also presented a less active appearance than did equivalent lesions in earlier groups. No renal lipomatous tumors were seen among the 100 mesenchymal neoplasms induced in this study, but a single lesion consistent with an early nephroblastoma was found in one rat dosed at birth. The exclusive occurrence of two predominant types of kidney tumor indicates the specificity of the host-tumor interaction elicited by dimethylnitrosamine. (24 refs)

- 79-6864 Lack of Proportionality Between Rate of Cell Division and Induction of Tumors in Carcinogen-exposed Regenerating Livers. (Eng) Becker, F. F. (Dept. Pathology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030). *Cancer Res* 39(12): 5177-5178; 1979.

Male CFE Sprague-Dawley rats underwent 70% hepatectomy at 55 or 175 g body wt, and the course of DNA synthesis of the first responsive wave of cell division was determined by [³H]thymidine incorporation and DNA analysis. Peak DNA synthesis occurred at the 20th-22nd hr for the younger rats and at the 24th-26th hr for the older ones. The specific activity of the older rats was 2.5 times greater than that of the older ones at peak synthesis. Dimethylnitrosamine (DMN: 10 mg/kg, ip) was administered to the older rats 24 hr after partial hepatectomy and at 6, 20, and 30 hr after surgery (9 mg/kg, ip) in the 55-g rats. 7,12-Dimethylbenz(a)anthracene (DMBA: 20 mg/kg, ip) and N-hydroxyacetylaminofluorene (40 mg/kg, ip) were given only to the younger rats at 6, 20, and 30 hr after operation. The animals were observed until they were 2 yr old. Primary hepatocellular carcinoma (PHC) was identified in 2/22 older rats treated with DMN and in 2/18 and 3/18 younger rats given DMN at 20 and 30 hr, respectively. PHC was not detected in any of the other rats. In these experiments, the use of the young rat, with its greatly increased amplitude and synchrony of DNA synthesis, did not commensurately increase the yield of carcinoma nor shorten the lag time significantly. These results suggest that carcinogen administration during cell division is not in itself sufficient to give a high yield of tumors. The results also suggest that the post-S period might be even more susceptible to DMN than the S phase. (14 refs)

- 79-6865 Correlation of DNA Methylation by Methyl(acetoxymethyl)nitrosamine with Organ-specific Car-

cinogenicity in Rats. (Eng) Kleihues, P. (Abteilung Neuropathologie, Pathologisches Institut der Universität, 78 Freiburg, W. Germany); Doerjier, G.; Keefer, L. K.; Rice, J. M.; Roller, P. P.; Hodgson, R. M. *Cancer Res* 39(12): 5136-5140; 1979.

Male Sprague-Dawley (Charles River CD) rats received a single iv or ip injection (12 mg/kg) of the α -acetoxymethyl derivative of dimethylnitrosamine, *N*-[¹⁴C]methyl-*N*-acetoxymethylnitrosamine (MAMN), and were killed after 12 hr. Following iv injection, highest concentrations of 7-methylguanine and O⁶-methylguanine were present in DNA of the lung, the principal target organ in MAMN carcinogenesis at this dosage by this route of application. Ip injection led to preferential DNA alkylation in organs bordering the abdominal cavity, with highest levels of methylated purines in the ileum and colon, the principal sites of tumorigenesis for this route of administration. Esterases potentially responsible for the bioactivation of MAMN in vivo were found in all organs investigated, with the highest levels of activity located in rat kidney and liver. Incubation of MAMN with DNA and esterases from rat kidney in vitro resulted in a pattern of methylated purines similar to that produced by *N*-methyl-*N*-nitrosourea and related methylating carcinogens; these agents, including dimethylnitrosamine, thus appear to exert their biological effects through a common alkylating intermediate. Pretreatment of rat liver extracts with the esterase inhibitor diisopropyl fluorophosphate (10⁻⁴ M) reduced both the decomposition of MAMN and DNA alkylation in vitro by more than 90%. (34 refs)

- 79-6866 Establishment of a Cell Culture Line from a Transplantable Rat Stomach Cancer Induced by *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine. (Eng) Kobori, O. (First Dept. Surgery, Faculty Medicine, Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan); Martin, F.; Martin, M.; Turc, C. *Cancer Res* 39(12): 5141-5146; 1979.

A cell line, termed BV9, was cultured from a transplantable rat stomach cancer originally induced in the glandular stomach of a Wistar rat by po administration of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. The monolayer cells, subcultured for more than 35 passages, revealed pleomorphic features. Chromosomal analysis showed hypertetraploidy (mode, 95), and marker chromosomes were present. Cultured cells were injected sc into cyclophosphamide-conditioned syngeneic rats and produced tubular adenocarcinomas resembling the original tumor. (24 refs)

- 79-6867 Mutagenicity of *N*-Methyl-*N'*-aryl-*N*-nitrosoureas and *N*-Methyl-*N'*-aryl-*N'*-methyl-*N*-nitrosoureas in Relation to Their Alkylating Activity. (Eng) Yano, K. (Dept. Chemistry, Saitama Medical Sch., 981 Kawakado, Moroyama, Iruma-gun, Saitama 350-04, Japan); Isobe, M. *Cancer Res* 39(12): 5147-5149; 1979.

The mutagenic activities of a series of *N*-methyl-*N'*-aryl-*N*-nitrosoureas (MANU) and *N*-methyl-*N'*-aryl-*N'*-methyl-*N*-nitrosoureas (MAMNU) were investigated in *Salmonella typhimurium* strain TA 1535. All MANU compounds had strong mutagenic potency without metabolic activation, and their effectiveness was even greater than that of *N*-methyl-*N*-nitrosourea. The mutagenicity at a given concentration of the compounds (3.35 $\times 10^{-2}$ μ mole) was compared with the chemical alkylating activity with 4-(*p*-nitrobenzyl)pyridine. A positive parallelism was observed in the cases of *N*-methyl-*N'*-(*p*-methoxyphenyl)-*N*-nitro-

sourea, *N*-methyl-*N'*-(*p*-methylphenyl)-*N*-nitrosourea, *N*-methyl-*N'*-phenyl-*N*-nitrosourea, and *N*-methyl-*N'*-(*p*-chlorophenyl)-*N*-nitrosourea, whereas this correlation broke down with *N*-methyl-*N'*-(*p*-acetylphenyl)-*N*-nitrosourea and *N*-methyl-*N'*-(*p*-nitrophenyl)-*N*-nitrosourea. These observations are discussed in terms of both the inductive effect and hydrogen-bonding nature of the substituents and the difference in the chemical and biologic processes. The MAMNU compounds, which are the methyl-substituted derivatives on the second nitrogen (*N'*), had no significant or weaker mutagenicity when compared to the corresponding MANU compounds; this result was also in agreement with the results of the chemical alkylation. The dose-response curves for the two classes of derivatives showed that all mutagenicities, except in the case of *N*-methyl-*N'*-phenyl-*N'*-methyl-*N*-nitrosourea, increased similarly in accordance with an increase in their concentrations, indicating that the lethal effect might not influence the observed mutagenicity. Mechanistically, it has been suggested that removal of the hydrogen on *N'* may be involved in the transition state of both the chemical and mutagenic actions of the MANU compounds. With the MAMNU compounds, however, further investigations are needed to elucidate the observed results; other factors, such as inductive and steric effects by the methyl group on *N'*, may also be of importance in their case. (25 refs)

79-6868 Kidney Tumors Induced in Rats by the Antischistosomal Drug Niridazole. (Eng) Bulay, O. (Epilepsy Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE 68105); Patil, K.; Wilson, R.; Shubik, P. *Cancer Res* 39(12): 4996-5002; 1979.

The induction of renal tumors by the antischistosomal drug niridazole observed in MRC rats was studied. Rats aged 6 to 8 wk were fed niridazole in the diet at four dosage levels: 0.1% (Group 1); 0.05% (Group 2); 0.025% (Group 3); 0.0125% (Group 4); and 0% (Group 5). The rats were allowed to die spontaneously and were autopsied. The life span of Group 1 was shortened by the tox-

ic effects of niridazole, whereas the animals given lower concentrations lived longer. The main target tissue was the kidneys, with tumors developing in this organ in 9/60 animals in Group 1, in 34/58 in Group 2, in 34/59 in Group 3, and in 30/60 in Group 4. Forestomach tumors occurred in a slightly higher incidence than in controls, while the incidences of other lesions were similar to those occurring spontaneously in control rats. Histologically, epithelial tumors were adenomas and adenocarcinomas comprising solid papillary, clear cell, and tubular types, with the latter type predominating. Seven mesenchymal tumors were found among the 107 renal epithelial neoplasms. High frequencies of severe nephrosclerosis occurred in both treated and control rats, but the extent and severity of nephrosclerotic changes were greater in the treated rats and appeared significantly earlier. This study indicates that nephrosclerosis plays a cofactor role in the experimentally induced kidney tumors and that continuous carcinogen administration is necessary to initiate kidney tumors. (44 refs)

See also:

*(Rev.): 79-6603, 79-6604, 79-6605, 79-6606, 79-6607, 79-6608, 79-6609, 79-6610, 79-6611, 79-6612, 79-6613, 79-6614, 79-6615, 79-6616, 79-6617, 79-6618, 79-6619, 79-6620, 79-6623, 79-6624, 79-6626, 79-6630, 79-6633.

*(Phys.): 79-6871, 79-6872, 79-6873, 79-6876, 79-6883, 79-6888, 79-6889, 79-6891, 79-6892, 79-6893, 79-6899, 79-6900, 79-6908, 79-6924.

*(Viral): 79-6963, 79-6969, 79-6999, 79-7011, 79-7017, 79-7044.

*(Immun.): 79-7066, 79-7070, 79-7080, 79-7088.

*(Path.): 79-7122, 79-7123, 79-7125.

*(Epid.-Biom.): 79-7138, 79-7141, 79-7143, 79-7144, 79-7145, 79-7154, 79-7155, 79-7156, 79-7159, 79-7165, 79-7171, 79-7173, 79-7174, 79-7175, 79-7176, 79-7177, 79-7179, 79-7181, 79-7182, 79-7184.

PHYSICAL CARCINOGENESIS

- 79-6869 Analysis of Dose-Response Patterns in Mutation Research. (Eng) Haynes, R. H. (Dept. Biology, York Univ., Toronto, Ontario M3J 1P3, Canada); Eckardt, F. *Can J Genet Cytol* 21(3): 277-302; 1979.

Stochastic assumptions were used to derive formal expressions for induced mutagenesis, and the Poisson distribution was used to analyze UV-induced forward and reverse mutations in haploid strains of the yeast *Saccharomyces cerevisiae*. The mutation yield (mutants per cell treated) and cell survival should be reported independently, as such data are of more value in mutation research than curves showing mutation frequency (mutants per survivor) only. Mutation yields, and in particular the position and magnitude of max yields, should be measured as carefully as possible as a means of verifying the apparent pattern of mutation induction kinetics suggested by double-logarithmic plots of mutation frequencies. For purely linear processes of mutation induction and exponential survival, the max mutant yield is known to occur as the LD₃₇ dose. However, for nonlinear kinetic patterns, the position and magnitude of the max yield shifts away from the LD₃₇ in mathematically predictable ways. For any given pattern of killing and mutation, the ratio of the max mutant yields plotted over lethal hit units for two mutagens is a convenient measure of their relative mutagenic efficiencies. (40 refs)

- 79-6870 Enhancement of Excision-Repair Efficiency by Conditioned Medium from Density-inhibited Cultures in V79 Chinese Hamster Cells. Evidence for Excision Repair as an Error-free Repair Process. (Eng) Nakano, S. (First Dept. Medicine, Kyushu Univ. Sch. Medicine, Fukuoka 812, Japan); Yamagami, H.; Takaki, R. *Mutat Res* 62(2): 369-381; 1979.

The effect of conditioned medium (CM) from density-inhibited cultures on UV-induced cell killing, mutation frequency, and the rate of DNA synthesis was studied using V79 Chinese hamster cells. CM from stationary-phase cultures did not influence the cloning efficiency of unirradiated cells, although cell growth was retarded and colony size reduced. CM significantly reduced the lethal effect of UV light ($p < 0.01$), a max increase in cell survival being observed with medium conditioned for 1 day. There was a continuous increase in cell survival with increasing exposure to CM up to 18 hr, after which the rate plateaued. The increase in cell survival was mediated by a repair mechanism other than caffeine-sensitive postreplication repair. In normal medium, the rate of DNA synthesis in normal cells increased exponentially, whereas in CM it was significantly suppressed. Similar results were obtained with UV-irradiated cells, except that DNA synthesis recovered 3-4 hr after irradiation. S-phase nuclei in normal medium were heavily labeled with [³H]thymidine, whereas those in CM showed relatively little labeling. The reduction in the fraction of S-phase cells could reflect a reduced rate of ongoing DNA synthesis in these cells. CM did not influence the spontaneous mutation frequency of V79 cells, and at equicytotoxic doses of UV, mutation frequencies in CM-treated cells were equal to the frequency in untreated cells. The data suggest that CM potentiates an error-free excision repair process, leaving fewer lesions available for error-prone postreplication repair. (42 refs)

- 79-6871 Photodynamic Cytotoxicity of Mammalian Cells Exposed to Sunlight-simulating Near Ultraviolet Light in the Presence of the Carcinogen 7,12-Dimethylbenz(a)anthracene. (Eng) Utsumi, H. (Radiation Biology Center, Kyoto Univ., Kyoto 606, Japan); Elkind, M. M. *Photochem Photobiol* 30(2): 271-278; 1979.

The coal-derived carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) was added in varying concentrations to cultures of V79 Chinese hamster, C3H mouse 10T1/2, and human HeLa cells. Photolethality induced by the sunlight-simulating emission from Westinghouse Sun Lamps [approx 290-400 nanomoles (nm)] was enhanced by DMBA only in the presence of O₂. Treatment of cells with DMBA after irradiation was without lethal effect; the endoperoxide of DMBA was ineffective both before as well as after irradiation, and DMBA incubation before far-UV exposure (254 nm) had a protective effect. Cells rendered photosensitive by incubation with DMBA rapidly lost their sensitivity (in <10 min at 37 C) when incubated in a DMBA-free soln containing serum, but maintained their sensitivity at least for several hours when a serum-free soln was used. Although DMBA enhanced light-induced killing of cells in all phases of the cycle, cells undergoing DNA synthesis were preferentially sensitized. The data indicate that photodynamic lethality was due to one or both of the following: (1) the reaction with DNA of DMBA radicals followed by oxidation, or DMBA-produced singlet oxygen; or (2) the peroxidation of lysosomal membranes followed by the release of hydrolases, including DNases. The results with DMBA + near-UV as a model representing the combined effects of sunlight and fossil-fuel derived polycyclic aromatic hydrocarbons are discussed in terms of altered cell properties (eg, neoplastic transformation) in sublethally affected cells. (59 refs)

- 79-6872 Photosensitized Reactions and Carcinogenesis. (Eng) Fry, R. J. (Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN 37830); Ley, R. D.; Grube, D. D. *Natl Cancer Inst Monogr* (50): 39-43; 1978.

The relationship between DNA cross-links induced by 8-methoxypsoralen (8-MOP) plus UV radiation and tumor induction was investigated in two strains of hairless mice, SKH:hairless-1 and HRS/J/An1. The mice were exposed to three light sources with emissions in the range 300-400, 320-400, and predominantly 365 nanometers (nm). 8-MOP was administered topically at doses of 250 µg 5x/wk for 24 wk, 3x/wk for 6 or 12 wk or 5x/wk for 7 wk followed by 10 µg 12-O-tetradecanoylphorbol-13-acetate (TPA) 3x/wk for 26 wk. In each case, UV radiation was administered 45-60 min after 8-MOP. In the SKH:hairless-1 mice, combined 24-wk treatment with 8-MOP and 320-400 nm UV resulted in a cumulative skin tumor incidence of approx 80%. The same irradiation without 8-MOP produced no epidermal carcinomas. The 300-400 nm range was the most tumorigenic spectrum range in the SKH:hairless-1 mice, but it produced no tumors in the HRS/J/An1 mice. The tumor incidence in mice receiving the combined treatment 3x/wk for 12 wk was markedly lower than in mice treated 5x/wk for 24 wk. When TPA was added after 12 wk of 3 exposures/wk to 8-MOP and 320-400 nm, the cumulative

tumor incidence was similar to that found with 24 wk of combined treatment without TPA promotion. The tumor response in the two strains was similar when TPA treatment followed the 8-MOP-UV exposures. Carcinoma induction by 8-MOP and 365-nm radiation suggested that psoralen photoadducts influenced tumor development. However, the strain differences in tumor incidence implied an apparent lack of relationship between psoralen DNA cross-links and tumorigenesis. It is stressed, however, that the differences in tumor incidence were due mainly to differences in expression rather than in initiation of tumors. (15 refs)

- 79-6873 Deoxyribonucleic Acid Repair Synthesis in Permeable Human Fibroblasts Exposed to Ultraviolet Radiation and N-Acetoxy-2-(acetylaminofluorene). (Eng) Roberts, J. D. (Dept. Pathology, Washington Univ. Sch. Medicine, St. Louis, MO 63110); Lieberman, M. W. *Biochemistry* 18(21): 4499-4505; 1979.

DNA repair synthesis was studied in permeable confluent normal and repair-deficient human fibroblasts using [^3H] deoxycytidine triphosphate (dCTP), bromodeoxyuridine triphosphate, deoxyATP, and deoxyguanosine triphosphate as substrates. Repair synthesis occurred as judged by the following criteria: (1) labeled nucleotides were incorporated into parental DNA ($p = 1.73 \text{ g/cm}^3$ in alkaline CsCl); (2) incorporation into parental DNA was negligible in the absence of damage and increased 10- to 20-fold in normal cells following exposure to ultraviolet radiation (UV) or the direct-acting chemical carcinogen N-acetoxy-2-(acetylaminofluorene); and (3) damage-dependent DNA synthesis was absent in preparations made from excision repair-deficient human diploid fibroblasts (xeroderma pigmentosum cells, complementation group A). The reaction was linear for 10 min and continued for at least 1 hr. Repair synthesis was stimulated at least fivefold by the addition of 5 mM ATP. It was strongly Mg^{2+} dependent, inhibited by NaCl, and only partially dependent upon the addition of exogenous deoxynucleotide triphosphates. The pH optimum in tris-HCl buffer was 7.6. Following UV damage, labeled deoxycytidine and deoxycytidine monophosphate were incorporated into parental DNA but at reduced levels (38 and 88%, respectively) compared to dCTP. The addition of $\beta\text{-NAD}^+$ (the naturally occurring isomer) or $\alpha\text{-NAD}^+$ (a competitive inhibitor) had little effect on repair synthesis in this system. By saturating the system with deoxynucleotide triphosphates and using published estimates of patch size, it was calculated that in this system a normal cell can put in a minimum of 100-900 repair patches/min. (51 refs)

- 79-6874 Photoreactivation: Evaluation of Pyrimidine Dimers in Ultraviolet Radiation-induced Cell Transformation. (Eng) Sutherland, B. M. (Dept. Biology, Brookhaven Natl. Lab., Upton, Long Island, NY 11973). *Natl Cancer Inst Monogr* (50): 129-132; 1978.

Conditions that must be met before photoreactivation can be used as an analytical test for determining the role of pyrimidine dimers in UV damage to mammalian cells include the following: the photoreactivating enzyme (PRE) must be present in all cells, act on pyrimidine dimers in DNA, act specifically on dimers, have access to cellular DNA and thus be able to monomerize dimers in intact cells, and be able to mediate restoration of biologic function. Evidence for each of these points is examined, with particular emphasis on areas in which further experimentation is critically necessary. Human fibroblasts containing PRE, which acts on

dimers and converts them to monomers, were exposed to UV radiation from a low pressure mercury lamp, allowed to grow, and tested for their ability to grow in soft agar. Increasing exposure to UV increased the number of colonies observed on the agar plate. Exposure to photoreactivating light yielded a substantial decrease in the number of colonies per plate. These preliminary results suggest that lesions leading to cell transformation are subject to photoreactivation and that pyrimidine dimers may be important in solar carcinogenesis. (28 refs)

- 79-6875 Clinical, Genetic and DNA Repair Studies on a Consecutive Series of Patients with Xeroderma Pigmentosum. (Eng) Pawsey, S. A. (Pediatric Res. Unit, Guy's Hosp. Medical Sch., London, England); Magnus, I. A.; Ramsay, C. A.; Benson, P. F.; Giannelli, F. *Q J Med* 48(190): 179-210; 1979.

Clinical, genetic, and biochemical findings are reported for 13 families with xeroderma pigmentosum (XP); the cases included 14 patients and 2 fetuses. Twelve of the 14 patients showed a decrease in unscheduled DNA synthesis following UV irradiation, which was consistent with a deficit in excision repair; two of these patients were brother and sister. The other two patients were defective in post-replication repair. The unscheduled DNA synthesis in skin fibroblast cultures from 7/13 parents of the XP patients did not differ significantly from that of controls, but significantly lower values were found in the other six. Somatic cell fusion was used to determine to which of seven different complementation groups the patients could be assigned. Three families belonged to complementation group A, four to group C, and six to group D. The unscheduled DNA synthesis of group A cells increased with UV dose (10-150 J/m^2) but after 105 min only very moderately with time. Group C cells showed only modest dose effects and increased synthesis with time up to 45 min. Group D cells also showed only a mild dose-response, but their increase in unscheduled DNA synthesis lasted for up to 6 hr. These differences indicate that mutations of different genes play a role in XP. XP patients are highly prone to skin cancer, which indicates that a defect in dimer excision repair or bypass of photolesions during DNA replication may predispose to actinic cancers. Chromosome rearrangements, mitotic errors, polyploidization, and perhaps even the transfer of chromosome segments may all contribute to the evolution of malignant cells. There is also the possibility of an immunological change in XP that results in a tolerance toward actinic cancers by favoring the release of tumor-associated antigens. (141 refs)

- 79-6876 Inhibition of Skin Carcinogenesis In Vivo by Caffeine and Other Agents. (Eng) Zajdela, F. (Institut National de la Sante et de la Recherche Medicale, Institut du Radium, Batiment 110, 91405 Orsay, France); Latarjet, R. *Natl Cancer Inst Monogr* (50): 133-140; 1978.

The inhibition of UV-induced skin cancer by caffeine and other postreplication-repair or excision-repair inhibitors was studied in Swiss (Carshalton) mice. The induction of skin cancer by repeated irradiation with UV-light was strikingly reduced by the local application of caffeine prior to each exposure. Theophylline displayed the same activity. These two substances have been selected as probable inhibitors of error-prone, postreplicative DNA repair. Conversely, redutone and chloroquine, which are considered as inhibitors of the error-free, prereplicative excision repair, did not modify the incidence of the tumors. Special em-

phases has been given to the histologic behavior of radiolabeled caffeine in the normal and UV-irradiated epidermis of the mouse in vivo and to the ability of mouse epidermal cells in vitro to repair DNA after UV irradiation. (32 refs)

- 79-6877 DNA Excision-Repair Processes in Human Cells Can Eliminate the Cytotoxic and Mutagenic Consequences of Ultraviolet Irradiation. (Eng) Maher, V. M. (Carcinogenesis Lab., Michigan State Univ., Fee Hall, East Lansing, MI 48824); Dorney, D. J.; Mendrala, A. L.; Konze-Thomas, B.; McCormick, J. J. *Mutat Res* 62(2): 311-323; 1979.

DNA excision-repair processes in diploid human fibroblasts were able to eliminate potentially cytotoxic and mutagenic lesions induced by UV radiation (254 nanomoles), as shown in either of two ways. Cells with normal rates of excision were compared with cells with an intermediate excision rate (XP2BE) and cells with an excision rate $\leq 1\%$ of the normal rate (XP12BE) for sensitivity to UV-induced killing and mutation. The normal cells proved resistant to UV doses which in XP cells reduced survival to 14% and 0.7%, respectively, and increased the frequency of mutations to 8-azaguanine resistance 5- to 10-fold over background. Cells in confluence were irradiated with cytotoxic and mutagenic doses of UV and allowed to carry out excision repair. After various lengths of time they were replated at lower densities to allow for expression of mutations to 6-thioguanine resistance and/or at cloning densities to assay survival. Normal cells and XP2BE cells exhibited a gradual increase in survival from an initial level of 15-20% to 100% if held approx 20 hr in confluence. In contrast, XP12BE cells showed no increase from an initial survival of 20% even when held for 7 days. Normal cells irradiated in confluence but prevented from replicating for 7 days exhibited background mutation frequencies, whereas the mutation frequency in XP12BE cells did not change with the time in confluence. (22 refs)

- 79-6878 Further Characterization of Immunological Unresponsiveness Induced in Mice by Ultraviolet Radiation. Growth and Induction of Nonultraviolet-induced Tumors in Ultraviolet-irradiated Mice. (Eng) Kripke, M. L. (Cancer Biology Program, NCI, Frederick Cancer Res. Center, Frederick, MD 21701); Thorn, R. M.; Lill, P. H.; Civin, C. I.; Pazmino, N. H.; Fisher, M. S. *Transplantation* 28(3): 212-217; 1979.

Specific-pathogen-free mice of several inbred strains were irradiated with UV light, their susceptibility to primary and transplanted tumors etiologically unrelated to UV radiation was compared with that of unirradiated mice. Although the UV-irradiated mice were unable to reject transplants of highly antigenic syngeneic tumors induced by UV light, the growth of syngeneic, non-UV-induced tumors generally was not accelerated in these animals. Furthermore, the UV-irradiated mice were no more susceptible to the induction of primary leukemias, mammary tumors, or sarcomas than were unirradiated animals. Tests of immune responses to weak transplantation antigens showed that UV-irradiated mice rejected H-Y-incompatible skin grafts as vigorously as did normal animals and that the primary in vitro cytotoxic responses of spleen cells from UV-irradiated mice to trinitrophenyl-modified syngeneic cells and to Hh antigens were unaffected. It is concluded that the susceptibility of UV-irradiated mice to challenge with UV-induced tumors represents a selective unresponsiveness, and that it is not attributable to a generalized deficiency in the immune response to tumor-specific antigens or to weak transplantation antigens. (26 refs)

- 79-6879 A Systemic Effect of Ultraviolet Irradiation and Its Relationship to Tumor Immunity. (Eng) Fisher, M. S. (Cancer Biology Program, Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701). *Natl Cancer Inst Monogr* (50): 185-193; 1978.

Chronic irradiation of mice with UV light produces a systemic alteration that is immunologic in nature and may be due to the presence of specific suppressor lymphoid cells. The immunologic aspect of this systemic alteration was demonstrated by cell transfer experiments. Lymphoid cells from UV-treated donors were unable to confer tumor resistance to lethally x-irradiated and neonatal liver reconstituted recipients, whereas recipients given lymphoid cells from normal donors were resistant to a challenge with a syngeneic UV-induced tumor. Therefore, lymphoid cells from normal donors could mediate tumor rejection, but lymphoid cells from UV-irradiated donors could not. Furthermore, lymphoid cells from UV-treated donors suppressed the ability of lymphoid cells from normal donors to mediate syngeneic tumor rejection when mixed 1:1 before transfer to lethally x-irradiated recipients. This suppression was specific since all recipients resisted an allogeneic UV-induced tumor challenge. Serum transfer experiments failed to demonstrate any inactivating or suppressive substances in the serum of UV-treated mice. These results suggest that UV-treated mice failed to reject UV-induced tumors because irradiation induced specific suppressor lymphoid cells that prevented the development of an immune response against tumor antigens. (5 refs)

- 79-6880 Ultraviolet Wavelength Regions Implicated in Toxic and Mutagenic Effects of Broad Spectrum Radiation from Fluorescent Lamps on L5178Y Mouse Lymphoma Cells. (Eng) Jacobson, E. (Div. Biological Effects, Bureau Radiological Health, FDA, HEW, 5600 Fishers Lane, Rockville, MD 20857); Krell, K. *Mutat Res* 62(3): 533-538; 1979.

Emitted light from four commercially available fluorescent lamps was tested for mutagenic and toxic effects on mouse L5178Y lymphoma cells in vitro in order to identify the region of the spectrum responsible for such effects of broad spectrum radiation from fluorescent lamps. Irradiance spectra were determined for wavelengths between 250 and 800 nanometers (nm) with special attention to the range 280-390 nm. Surviving fraction (toxicity) and mutations per 10^5 surviving cells (mutagenicity) were reported after exposure of cultures (at 8 cm distance for a period of time allowing for uniform dose) to filtered or unfiltered light from each lamp. No single wavelength was found to be particularly responsible for mutagenicity or toxicity. It is suggested that relative intensities of several wavelengths in the UV and near UV region may be responsible and that different portions of the spectrum may be involved in mutagenesis and toxicity. (7 refs)

- 79-6881 Workshop on Production and Measurement of Ultraviolet Light: Light Sources for Solar Simulation in Photocarcinogenesis Studies. (Eng) Forbes, P. D. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140). *Natl Cancer Inst Monogr* (50): 91-95; 1978.

Light sources for solar simulation in photocarcinogenesis studies include the xenon lamp fitted with a borosilicate filter, an infrared (IR)-absorbing glass filter, or a Schott glass filter. The advantages and disadvantages of each filter system used are discussed. Current

experiments are using the Schott WG 320 filter to give the same Robertson-Berger (sunburn meter) reading as IR-absorbing filters while solving problems concerning light quantity and light quality. Since the WG 320 filtered system is known to produce tumors in mice, it will be useful in examining possible interactive effects of the solar spectrum. (8 refs)

- 79-6882 Action Spectrum for Ultraviolet Carcinogenesis. (Eng) Freeman, R. G. (Dept. Pathology, Univ. Texas Health Sciences Center, Midwestern Medical Sch., Dallas, TX 75235). *Natl Cancer Inst Monogr* (50): 27-29; 1978.

High-intensity monochromatic UV wavelengths of 290-320 nanometers (nm) were compared for their efficacy in inducing tumors in mice, to test the hypothesis that carcinogenic effectiveness was proportional to erythral activity. Groups of albino mice were exposed to the UV light 3x/wk on one ear with the opposite ear serving as control. The experiment was halted when 50% of the surviving animals developed tumors. UV irradiation at 300 nm produced skin tumors, but radiation at 310 nm did not. In the 300-nm group, the first tumor appeared after 323 days, and 50% of the animals developed tumors by 458 days. All of the tumors were squamous cell carcinomas. A second series of experiments was performed in which the mice were exposed to UV at 290, 310, and 320 nm in dosages proportional to the threshold dose for erythema production in untanned human skin. At 310 nm, no tumors were observed in mice exposed to low levels [60 millijoules (mJ)/cm²/wk]; at high levels (750 mJ/cm²) tumors were induced, and their first appearance and time at which 50% of the survivors developed tumors paralleled the responses of mice receiving 60 mJ/cm²/wk at 300 nm. The 8 tumors in the 16 survivors included 5 squamous cell carcinomas, 2 fibrosarcomas, and 1 angiosarcoma. Tumors were also observed after 417 and 464 days, in 2/5 mice receiving UV energy at 320 nm. No tumors of visible damage occurred in mice exposed to UV at 290 nm. These results demonstrate that the carcinogenicity of UV is proportional to its erythral potency. (13 refs)

- 79-6883 Ultraviolet Light in the Oncogenic Transformation of Cultured C3H/10T1/2 Mouse Embryo Cells. (Eng) Mondal, S. (Univ. Southern California Cancer Center, Los Angeles, CA 90031); Heidelberg, C. *Natl Cancer Inst Monogr* (50): 71-73; 1978.

A mouse embryo fibroblast line, C3H/10T1/2, that can be transformed by chemical carcinogens, x-irradiation, UV radiation, and oncornavirus was developed. When these cells were irradiated with 10, 25, 50, 100, 150, or 200 ergs/mm² of UV light, neither transformation nor cytotoxicity was observed at the two lower doses. When the irradiated cells were cultured in medium containing tetradecanoylphorbol acetate (TPA: 0.1 µg/ml) starting from 0-120 hr after irradiation, a high frequency of transformation was always produced. When the cells were initiated with subeffective concentrations of 3-methylcholanthrene (0.1 µg/ml) followed by UV radiation at different intervals, no transformation occurred; however, these initiated cells were transformed after TPA treatment. No transformation occurred when the cells were treated with multiple exposures to UV light, nor when the cells were treated with TPA followed by UV irradiation at different intervals. UV in this system acts as a pure initiator in the two-stage process of oncogenic transformation. (15 refs)

- 79-6884 Experimental Ultraviolet Photocarcinogenesis: Wavelength Interactions and Time-Dose Relationships. (Eng) Forbes, P. D. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Health Sciences Center, Philadelphia, PA 19140); Davies, R. E.; Urbach, F. *Natl Cancer Inst Monogr* (50): 31-38; 1978.

Variables that affect quantitative models of UV photocarcinogenesis were studied in SKH hairless mice. Skin tumors were induced in these mice by exposure to fluorescent FS sun lamps or to a long-arc xenon solar simulator. Tumors developed about equally well with varying amounts of UV-A radiation ($\lambda > 320$ nm) led to substantial increases in carcinogenic effectiveness. A tumor-initiating dose of UV-B (280-320 nm; 4-10 wk of daily FS lamp exposures) was rendered less effective by subsequent exposures of the mice to UV-A (6 hr/day, F-40 T12BL lamps). Most tumors induced by a short course (10 wk) of FS lamp exposure grew slowly or regressed, whereas mice exposed for a longer period (30 wk) developed more tumors, and many of those that appeared early grew aggressively. The effects of daily dose fractionation were less clear. The above variables, as well as others, are being tested in a program designed to yield useful information on the effects of changing spectrum, dose, and dose-delivery rates on sunlight-induced cancer. (17 refs)

- 79-6885 Life History and Histopathology of Ultraviolet Light-Induced Skin Tumors. (Eng) Stenback, F. (Dept. Pathology, Univ. Kuopio, Harjulantie 1, 70100 Kuopio 10, Finland). *Natl Cancer Inst Monogr* (50): 57-70; 1978.

Histologic, histochemical, and ultrastructural methods were used to study the immediate and long-term effects of UV irradiation of different wavelengths on the skin of NMR rats, outbred female Swiss mice, and Syrian golden hamsters. High-intensity UV light of medium wavelengths produced hyperplasia and papillomas, as well as a dysplastic, intermediary solar keratosis-like stage, with distinct cellular atypia leading to several types of squamous cell carcinomas. High doses of UV irradiation of short duration caused scars, which developed into fibromas and fibrosarcomas composed of "light" and "dark" cells. Carcinomas with neoplastic squamous and fibrous components were uncommon; however, collision tumors with two components were occasionally seen. Angiomas and angiosarcomas with a proliferating endothelial structure were observed, but adnexal tumors, with follicular or sebaceous differentiation, and basal cell carcinomas were infrequent. Pigment-cell tumors were rarely found. The number of tumors and tumor-bearing animals at different stages of the experiment were also studied. Tumors were compared with lesions induced by chemical carcinogens in different systems. UV carcinogenesis was characterized by many tumor-bearing animals, but with a low total tumor count and a high mortality, thereby decreasing the number of animals-at-risk. The tumor types, their progression from one type to another, and the distribution of certain biologic characteristics were also analyzed. It is concluded that UV irradiation is an effective tumor inducer in animal skin and that the type of tumor, its behavior, and its location depend on the experimental conditions. (29 refs)

- 79-6886 Influence of Heat, Wind, and Humidity on Ultraviolet Radiation Injury. (Eng) Owens, D. W. (Kelsey-Seybold Clinic, 6624 Fannin St., Houston, TX 77030); Knox, J. M. *Natl Cancer Inst Monogr* (50): 161-167; 1978.

The influence of heat, wind, and humidity on the acute and chronic skin damage caused by UV radiation (UVR) to mice housed in environmental chambers and irradiated under controlled conditions was investigated. Hairless HRS/J mice irradiated at room temperature (71 F) developed distinct erythema and small scaling areas by the third day after irradiation. Those irradiated after their skin had been heated to 98 F developed more intense erythema, crusting and necrosis. Animals irradiated after cooling of their skin to 58 F developed only mild erythema and small scaling areas. In experiments concerning environmental temperature, Swiss albino mice demonstrated an increased number and rate of tumor development when kept at 90 F than those kept at room temperature. Swiss albino mice exposed to UVR and wind had greater skin damage than those exposed to radiation alone. Wind also accelerated tumorigenesis in mice that received chronic UVR. Hairless HRS/J mice exposed to high humidity (80%) had more severe skin damage after UVR than those kept at low humidity (5%). Mice kept at high humidity and irradiated developed skin tumors earlier (day 76) than those kept at low humidity (20%; day 154). Since heat, wind, and humidity enhance acute as well as chronic UV injury and carcinogenesis, these influences should be considered in any biologic experiment on UV injury. (11 refs)

- 79-6887 Immunologic Aspects of Tumor Induction by Ultraviolet Radiation. (Eng) Kripke, M. L. (Cancer Biology Program, Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701); Fisher, M. S. *Natl Cancer Inst Monogr* (50): 179-183; 1978.

The general immune competence of UV-treated animals was tested in various in vivo and in vitro assays. These responses included tumor allograft rejection, skin graft rejection, antibody production against sheep RBC, graft-vs-host reactivity, delayed hypersensitivity to dinitrochlorobenzene, inflammatory response, lymphocyte blastogenesis, and macrophage functions. Chronic treatment of mice with UV radiation induced skin cancer and produced a systemic change that interfered with host resistance against these tumors. After a short course of UV radiation, the UV-irradiated mice lost their ability to reject transplanted UV-induced tumors, even though such transplants were rejected by unirradiated animals. The growth of the transplanted tumors in UV-treated mice was attributed to a systemic alteration in animals induced by UV irradiation of the skin. UV-irradiation does not appear to decrease host resistance against all syngeneic tumors per se, or even against all syngeneic fibrosarcomas; three dermal tumors grew more rapidly in UV-treated mice. Whether this acceleration is immunologically mediated and stems from antigenic similarities among these and UV-induced tumors, or whether this is due to the physiologic effects of UV treatment on the host is unknown. (21 refs)

- 79-6888 Effect of Dietary Cholesterol on Ultraviolet Light Carcinogenesis. (Eng) Black, H. S. (Photobiology Lab., Building 203, Rm 134, Veterans Admin. Hosp., Houston, TX 77211); Henderson, S. V.; Kleinhans, C. M.; Phelps, A. W.; Thornby, J. I. *Cancer Res* 39(12): 5022-5027; 1979.

Several levels of dietary cholesterol, as well as antioxidant additives, were tested for their effect on ultraviolet light (UV) carcinogenesis. Hairless mice were divided into 12 groups of 50 animals each. The animals received a restricted, semipurified, isocaloric diet containing 0, 0.01, and 2% cholesterol with or without addition of a 2% (w/w) antioxidant mixture. A regimen of

escalating UV irradiation was used until a cumulative dose of 145 joules/cm² had been delivered. Animals were evaluated weekly for actinic lesions and biweekly for body wt, hematocrits, and serum cholesterol levels. A cumulative distribution frequency, based upon the asymptotic theory of extreme values, was used to determine tumor occurrence with time of study. Tumor development time for 50% of the animals for each dietary cholesterol level used was significantly different, with a longer development period occurring with increasing cholesterol level. Dietary antioxidants significantly suppressed UV-induced tumor formation, although this effect was not as pronounced as that seen in previous studies with commercial diets. The data indicate that dietary cholesterol does not enhance UV carcinogenesis but rather has a slight, but significant, moderating effect. This effect could result from direct participation of dietary cholesterol in the carcinogenic process or, alternatively, could occur as the result of sterol-altered epidermal parameters which effectively diminish the UV dose reaching target sites. (37 refs)

- 79-6889 Enhancement of Experimental Photocarcinogenesis by Topical Retinoic Acid. (Eng) Forbes, P. D. (Center Photobiology, Skin and Cancer Hosp., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Urbach, F.; Davies, R. E. *Cancer Lett* 7(2/3): 85-90; 1979.

Groups of hairless albino mutant mice (30 males, 30 females) received daily topical applications of all trans-retinoic acid (RA) starting at 7 wk of age for 30 wk (group A, methanol only; group B, 0.001% RA; and group C, 0.01% RA). Another group was treated with 0.1% croton oil daily (group D). Starting on the 1st day of croton oil treatment and the 15th of RA, each application was preceded by a 2-hr exposure to a xenon arc filtered through 2 mm of Schott WG 320 glass (approx equivalent in human erythema effectiveness to 5 min of mid-summer noon solar exposure in northern mid-latitudes). Tumors >1 mm in diameter first appeared in group A at 38 wk, group B at 21 wk, group C at 20 wk, and group D at 26 wk. At wk 55, animals in group A had 0.65 tumors/survivor; in group B, 6.3 tumors/survivor; in group C, 9.22 tumors/survivor; and in group D, 0.89 tumors/survivor. Skin tumors were histologically diagnosed as carcinoma in situ or squamous cell carcinoma. No metastases were detected. Slight scaling and flaking of the skin, but no gross evidence of erythema or irritation, was noted in RA-treated groups. These results indicate that topical application of RA to the skin of albino hairless mice significantly enhances the carcinogenic effectiveness of simulated sunlight. (22 refs)

- 79-6890 Pyrimidine Dimer Excision in Human Cells and Skin Cancer. (Eng) Regan, J. D. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Carrier, W. L.; Smith, D. P.; Waters, R.; Lee, W. H. *Natl Cancer Inst Monogr* (50): 141-143; 1978.

Three methods were compared for estimating the induction and removal of UV-induced pyrimidine dimers from the DNA of human fibroblasts (normal, xeroderma pigmentosum, and Fanconi's anemia). The approaches included pyrimidine-dimer chromatography that directly measured the percent of labeled thymidine existing as dimers in acid-insoluble DNA, a UV endonuclease incubation that induced a single-strand break next to and in the same DNA strand as the pyrimidine dimer, and bromodeoxyuridine (BrdUrd) photolysis, which estimated the number of pyrimidine dimers removed and repaired by excision

resynthesis and rejoining and the av size of the repair region for each dimer removed. All three methods indicated that after UV doses of 5-20 Joules/m², 50% of the dimers are removed by 24 hr. Almost complete excision is observed when the cells are incubated for periods of ≥ 72 hr after a dose of 5 Joules/m². The dimers are removed slowly by excision repair, and repair must operate actively for 3-4 days to remove all the dimers. (17 refs)

- 79-6891 Transformation Frequency of Syrian Golden Hamster Cells and Its Modulation by Ultraviolet Irradiation. (Eng) DiPaolo, J. A. (Biology Branch, Carcinogenesis Program, Div. Cancer Cause Prevention, NCI, Bethesda, MD 20205); Donovan, P. J. *Natl Cancer Inst Monogr* (50): 75-82; 1978.

Experiments in which UV radiation (253.7 nm) exposure of Syrian golden hamster cells seeded for colony formation caused an induction of transformation without any other insult are reported. Analysis of the quantitative data demonstrated a lack of a threshold response and a transformation frequency proportional to UV dose. No transformation occurred in unirradiated colonies. When cells seeded for colony formation were exposed to UV and subsequently treated with N-acetoxy-2-acetyl aminofluorene (AcAAF), a carcinogen known to induce UV-like damage, neither an additive nor a synergistic effect occurred. Caffeine at nontoxic concentrations potentiated lethality caused by AcAAF and also increased the number of colonies transformed by AcAAF when added post-AcAAF. The addition of a constant amount of caffeine (50 μ g/ml) for 48 hr at different intervals after carcinogen treatment resulted in max enhancement (10- to 17-fold) when added 4 hr post-AcAAF. UV-associated transformation was enhanced by pretreating the cells with a nontransforming dose of x-irradiation 48 hr before UV. The increase in transformation frequency was 6- to 12-fold per colony and 3- to 6-fold per dish. (21 refs)

- 79-6892 Description and Application of a Personal Ultraviolet Dosimeter: A Review of Preliminary Studies. (Eng) Challoner, A. V. (Dept. Physics, St. John's Hosp. Diseases of the Skin, Homerton Grove, London, England); Corbett, M. F.; Davis, A.; Diffey, B. L.; Leach, J. F.; Magnus, I. A. *Natl Cancer Inst Monogr* (50): 97-100; 1978.

Preliminary investigations of a dosimeter that can be used to measure individual exposures to UV radiation are described. The method is based on the use of polysulfone film, which, on exposure to UV, shows a change in absorbance that can be determined spectrophotometrically. Medical applications of the dosimeter are discussed. It is concluded that a personal film badge dosimeter gives information that complements that from a static electronic monitor and that such dosimeters would be useful for epidemiologic studies of UV-induced skin cancer. (12 refs)

- 79-6893 Effect of Antipain on Radiation Induction of Endogenous Type-C Virus from Mouse Cells In Vitro. (Eng) Niwa, O. (Dept. Experimental Radiology, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan); Sugahara, T. *Intervirology* 12(2): 120-123; 1979.

The effect of antipain (AP) on the radiation-induced expression of endogenous type-C virus from K-Balb mouse cells was studied in vitro. Incubation with antipain (≤ 5 mM) for 24 hr did not modify the plating efficiency, or x-ray sensitivity of the K-Balb cells or the

UV sensitivity of mouse L cells. However, UV- or x-ray-induced virus expression was markedly reduced by postirradiation treatment with antipain concentrations as low as 0.1 mM; the max level of inhibition was attained at concentrations higher than 5 mM. Spontaneous induction was also suppressed by antipain, but bromodeoxyuridine-induced virus expression was unaffected by the drug at concentrations up to 10 mM. Less than 4 hr postirradiation, treatment with antipain was sufficient to cause max inhibition of radiation-induced virus expression. The data suggest that a proteolytic step is involved in the radiation induction of endogenous type-C virus, while a different mechanism such as altered binding affinity of chromatin protein to DNA might be responsible for virus expression induced by halogenated pyrimidines. (19 refs)

- 79-6894 Role of Photosensitization and Oxygen in Chromosome Stability and "Spontaneous" Malignant Transformation in Culture. (Eng) Sanford, K. K. (Lab. Cellular and Molecular Biology, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, Bethesda, MD 20205); Parshad, R.; Jones, G.; Handleman, S.; Garrison, C.; Price, F. J. *Natl Cancer Inst* 63(5): 1245-1255; 1979.

The enhancement of both chromosome instability and malignant transformation of mouse cells in culture by visible light and oxygen was investigated. Nine cell lines were initiated from eight pools of 10- to 13-day C3H embryos. Each cell line was divided into sublines, which were either maintained shielded from light or were exposed for 3 or 24 hr to fluorescent light (approx 150 foot-candles) 2 or 3x/wk. Cultures of the sublines were also maintained with either a gaseous phase of 0-1% oxygen or atmospheric (18%) oxygen. Each line was monitored for cytologic manifestations of malignant neoplastic transformation, and eight lines were monitored for chromosome alterations. Seven lines were assayed for tumorigenicity by intraocular implantation into syngeneic hosts. Repeated light exposure and/or a high level of oxygen increased the frequency of minute chromosomes, which result from chromatid breaks, and also increased the rate of shift from the diploid to the heteroploid state. Four cell lines showed no cytologic changes indicative of neoplastic change during the test period. Two of these were assayed in vivo and failed to grow as tumors. In the remaining six lines, neoplastic colonies appeared earlier or more abundantly in light-exposed cultures and/or those gassed with high oxygen. In three of these lines, tumors developed only from light-exposed cultures; in the other two, tumor latency periods were significantly shorter in cultures exposed to light or gassed with atmospheric oxygen. (41 refs)

- 79-6895 A Negative Test for Mutagenic Action of Microwave Radiation in *Drosophila melanogaster*. (Eng) Hamnerius, Y. (Res. Lab. Electronics, Chalmers Univ. Technology, Goteborg, Sweden); Olofsson, H.; Rasmuson, A.; Rasmuson, B. *Mutat Res* 68(3): 217-223; 1979.

The mutagenicity of microwave radiation [2,450 MHz continuous waves (CW)] was tested in *Drosophila melanogaster*. Embryos in water were exposed to the electromagnetic field with a mean specific absorption rate of 100 W/kg. A sensitive somatic test system was used, in which mutagenicity was measured as the frequency of somatic mutations for eye pigmentation. In this test system, microwaves showed no mutagenic activity. (19 refs)

- 79-6896 **Experimental Squamous Cell Lung Tumors in Sprague-Dawley and Murine Pneumonitis-free Rats.** (Eng) Gracey, D. R. (Mayo Clinic, Rochester, MN 55901); Fish, J. E.; Divertie, M. B. *Cancer* 44(2): 598-603; 1979.

Radioactive pegs (ruthenium-105/rhodium-106 microspheres embedded in a polyurethane peg) were placed in the lungs of 32 pathogen-free rats and 28 Sprague-Dawley rats, and the animals were killed 12-13 wk after implantation. In 11/32 pathogen-free rats with radioactive pegs, lung tumors, histologically and ultrastructurally resembling well-differentiated squamous cell bronchogenic carcinomas, developed after an av of 139 days. None of the pathogen-free rats with nonradioactive pegs developed tumors. Fifteen Sprague-Dawley rats with radioactive pegs showed well-differentiated squamous cell carcinoma after an av of 147 days. No evidence of metastases to extrapulmonary tissue was observed. The difference between the time of exposure and development of neoplasms between the specific pathogen-free and the Sprague-Dawley rats that received radioactive pegs was not significant. Various degrees of murine pneumonitis were present in all Sprague-Dawley rats, but this was not seen in the specific pathogen-free rats. These results indicate that murine pneumonitis is not a prerequisite for the development of neoplasia produced by point-source irradiation. The histologic and cytologic features of this experimental tumor are consistent with the appearance of a highly differentiated invasive bronchogenic squamous cell tumor in man, making this a valuable model for the study of this disease. (13 refs)

- 79-6897 **Intrinsic and Extrinsic Variables Affecting Sensitivity to Radiation Carcinogenesis.** (Eng) Yuhas, J. M. (Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM 87131). *Int J Radiat Oncol Biol Phys* 5(7): 1117-1122; 1979.

The linear *plus* quadratic model, which is particularly useful in radiation carcinogenesis, is examined in terms of the types of injury that can contribute to it and in terms of its reliability in predicting the effects of dose protraction. Through the analysis of simple experimental systems, it is demonstrated that $aD + bD^2$ kinetics can result from injury to the cells that eventually develop into cancer (target cells) or from injury to cells that affect target cell survival. These kinetics can fail to predict the consequences of dose protraction, which is largely due to the fact that transformation increases with dose whereas survival decreases. The role of these models in helping to develop an understanding of mechanisms should therefore be restricted to the formulation of basic hypotheses, which are subject to direct testing in the laboratory. (21 refs)

- 79-6898 **In Vitro Neoplastic Transformation of Plant Callus Tissue by γ -Radiation.** (Eng) Pandey, K. N. (Thomas Hunt Morgan Sch. Biological Sciences, Univ. Kentucky, Lexington, KY 40506); Sabharwal, P. S. *Mutat Res* 62(3): 459-465; 1979.

Tumors have been induced by ^{60}Co - γ -radiation (100-3,000 rads) in callus tissue derived from a monocotyledonous flowering plant (*Haworthia mirabilis* Haw.). The transformed tissue exhibited compact texture, excessive cell proliferation and loss of capacity for organogenesis. Tumors were characterized by their ability to undergo continuous autonomous growth on minimal media in the subsequent four generations of subculture. In contrast, the nonir-

radiated control tissue grew with friable texture, required inositol or growth hormones, and showed prolific differentiation of vegetative buds. (17 refs)

- 79-6899 **Micronuclei Induced by X-Rays and Chemical Mutagens in Meiotic Pollen Mother Cells of Tradescantia. A Promising Mutagen Test System.** (Eng) Ma, T. H. (Dept. Biological Sciences, Western Illinois Univ., Macomb, IL 61455). *Mutat Res* 64(5): 307-313; 1979.

In *Tradescantia* species, pollen mother cells of each of the buds of an inflorescence are synchronized at different meiotic stages, thus facilitating the treatment of the appropriate buds containing only the mutagen-sensitive, prophase stage. Damage to chromosomes at early prophase can be determined by scoring the frequency of micronuclei (MCN) in tetrads 24-30 hr after treatment. The high efficiency and the versatility of this 'MCN-in-Tetrad' test system were demonstrated for radiation and for chemical mutagens. When inflorescences of the plant cuttings were exposed to 20 and 40 R of x-rays, an av of 22.8 and 66.6 MCN/100 tetrads were observed respectively. Liquid ethyl methanesulfonate (EMS) at 50 and 100 mM absorbed through the stem induced 13.2 and 15.2 MCN/100 tetrads respectively, while gaseous EMS (1000 ppm) induced 17.4 MCN/100 tetrads. Liquid sodium azide (NaN_3), at 0.2 mM induced 10.1 MCN/100 tetrads, while 136 ppm of gaseous hydrazoic acid (HN_3), which is the fume released from NaN_3 reacted with acid, induced 21.2 MCN/100 tetrads. The control of each of the experimental groups yielded around 5 MCN/100 tetrads. (18 refs)

- 79-6900 **Teratogenic Interaction of Hyperthermia and Vitamin A.** (Eng) Ferm, V. H. (Dept. Anatomy/Cytology, Dartmouth Medical Sch., Hanover, NH 03755); Ferm, R. R. *Biol Neonate* 36(3/4): 168-172; 1979.

The teratogenic effects of hyperthermia (39.5 C for 60 min) and vitamin A (5,000 U/100 g by stomach tube) were tested in LVG hamsters treated on day 8 of gestation. Heat alone caused a malformation rate of 7.5%, by day 13 of gestation, 8/24 litters showing at least one malformation. Vitamin A caused a malformation rate of 3.3%, 6/25 litters showing at least one fetus with an abnormality. Heat plus vitamin A caused a malformation rate of 36.4%, 22/25 litters showing one or more fetuses with malformations. All six litters treated with 20,000 U/100 g vitamin A alone had one or more abnormal fetuses, and 78.8% of the surviving fetuses from these litters were malformed. Exencephaly, encephalocele, and defects of the eye, face, lip, ribs, and tail were observed. The data suggest that maternal hyperthermia may be an important synergistic factor for a variety of potentially teratogenic influences during pregnancy. (15 refs)

- 79-6901 **Acoustic Neurinoma After Irradiation: Report of a Patient Treated for Facial Acne and Thyroid Carcinoma.** (Eng) Rhie, F. H. (E. P. Joslin Res. Lab., Harvard Medical Sch., Boston, MA); Zellmann, H. E. *Lahey Clin Found Bull* 27(4): 142-146; 1978.

The development of an acoustic neurinoma 8 yr after thyroidectomy and therapeutic irradiation for papillary carcinoma of the thyroid and metastases in a 27-yr-old woman is reported. At age 12 yr, the patient had undergone 16 courses of facial irradiation for

PHYSICAL CARCINOGENESIS

acne. Headache and facial numbness developed 4 yr after therapeutic irradiation for the thyroid carcinoma, suggesting the presence of acoustic neurinoma at this time, although positive diagnosis was not made until 4 yr later. It is suggested that the thyroid carcinoma and acoustic neurinoma were related to the patient's initial facial irradiations. (13 refs)

- 79-6902 An Intracranial Sarcoma Following Radiation of a Hypophyseal Adenoma. (Ger) Gerlach, H. (Pathologisches Institut des Bereichs Medizin, Martin-Luther-Universität, Leninalle 14, DDR-402 Halle, W. Germany); Janisch, W. *Zentralbl Neurochir* 40(2): 131-133, 135-136; 1979.

An intracranial fibrosarcoma was diagnosed at the autopsy of a 47-yr-old woman who had undergone radiation therapy (RT) for hypophyseal adenoma beginning 24 yr previously. The first RT series was 50% of the skin-erythema dose, given 14 times. Ten yr later, 2,500 rads were given to each (right and left) temporal field for symptoms of recurrence. The tumor recurrence was removed surgically 15 yr after the original diagnosis and identified as a chromophobic adenoma. Later, diabetes insipidus and severe headaches developed. The sella region was no longer discernible by x-ray. RT (1,000 rads/session) was begun, but the patient died before the planned therapy was completed. Her sella turcica region was occupied by a tennis-ball sized tumor containing collagen fibers and anaplastic spindle-type cells with atypical mitoses. The numerous mitoses may have resulted from the recent RT. Some traces of hypophyseal adenoma were found within the fibrosarcoma. No metastases were found. Twelve other cases of similar tumors developing after RT for hypophyseal adenomas were found in the literature, with an av latency of 10 yr (3-20 yr range). The finding of adenoma-cell nests in all areas of the sarcoma may indicate that the sarcoma arose in the stroma of the first tumor. (10 refs)

- 79-6903 X-Ray or γ -Ray Leukemogenesis in Mouse. (Eng) Rosen, P. (Hasbrouck Lab., Univ. Massachusetts, Amherst, MA 01003). *Med Hypotheses* 5(10): 1141-1144; 1979.

A theoretical model is presented for x-ray or γ -ray leukemogenesis in the mouse. The first step, a double strand break in the viral part of the genome, leads to constitutive production of the viral protein responsible for transformation by derepression of its operator control region. The second step involves binding of viral protein to the regulator gene of a two repressor system: binding to the gene of the first repressor leads to synthesis of the second, which will repress the expression of the leukocyte maturation gene. Results are compared with experimental results on CBA mice, and good agreement is found. (15 refs)

- 79-6904 X-ray Induced DNA Double Strand Break Production and Repair in Mammalian Cells as Measured by Neutral Filter Elution. (Eng) Bradley, M. O. (Lab. Experimental Pathology, Human Tissue Section, NCI, NIH, Bethesda, MD 20205); Kohn, K. W. *Nucleic Acids Res* 7(3): 793-804; 1979.

A neutral filter elution method for detecting DNA double strand breaks in mouse L1210 cells after x-ray is described. The assay detects the number of double strand breaks induced by as little as 1,000 rad of x-ray. The rate of DNA elution through the filters under neutral conditions increases with x-ray dose. Certain condi-

tions for deproteinization, pH, and filter type were shown to increase sensitivity. Hydrogen peroxide and bleomycin also induced apparent DNA double strand breaks, although the ratios of double to single strand breaks varied from those produced by x-ray. The introduction of double strand cuts by Hpa I restriction endonuclease in DNA lysed on filters resulted in a rapid rate of elution under neutral conditions, implying that the method can detect double strand breaks if they exist in the DNA. The eluted DNA banded with a double stranded DNA marker in cesium chloride, suggesting that the assay does detect DNA double strand breaks. L1210 cells were shown to rejoin most of the DNA double strand breaks induced by 5-10 krad of x-ray with a half-time of about 40 min. (11 refs)

- 79-6905 Basiliomas After Radiation Treatment of Hemangiomas. (Ger) Hadlich, J. (Hautklinik der Medizinischen Akademie Erfurt, Klement-Gollwald Strasse 34, DDR-508 Erfurt, E. Germany); Linse, R. *Dtsch Gesundheitswes* 34(10): 447-449; 1979.

Two cases are described in which basiliomas developed at the site of radiation treatment for a childhood hemangioma. A 16-yr-old girl presented with a tumor of irregular lumps within an area of radiation damaged skin on her back. She had been treated for hemangioma in this back area at age 2 yr. The second patient was irradiated at age 1 yr for hemangioma on her neck. At age 24 yr she noted a lesion in this area which sometimes oozed. When she came for treatment 1 yr later the lesion was ulcerated. Recent studies show the spontaneous regression rate of hemangiomas to be 80%-90%, and that radiation treatment does not significantly increase this rate. Thus radiation for childhood hemangiomas is not recommended. Freezing the area with CO₂ snow or liquid nitrogen should be tried for those that do not regress. Radiation damaged skin should be regarded as a precancerous condition. Small areas of damaged skin should be surgically removed. Patients with areas too large to be removed should be carefully followed. (28 refs)

- 79-6906 The significance of Leucocytosis in the X-irradiated Tumour-Bed. (Eng) Engel, D. (Pathology Dept., Univ. Zurich, Zurich, Switzerland). *Strahlentherapie* 155(9): 637-643; 1979.

Tumor growth and leukocytosis were studied in inbred NMRI mice subjected to x-irradiation (900 Rad) of the right loin-thigh area 1-30 days before the sc implantation of Ehrlich's mouse carcinoma into the irradiated and nonirradiated loin-thigh areas. The total tumor wt on the irradiated side (69.24 g) was approx half that of the nonirradiated control side (122.11 g). The number of leukocytes increased rapidly in the irradiated area during the first 24 hr after irradiation, then rapidly decreased to near normal by the fifth day after irradiation. Inflammation was never observed on the control side. The inhibitory effect of x-irradiation on tumor growth and the inflammatory response of the skin did not run a parallel course except during the first few days after irradiation, suggesting that hyperleukocytosis of the tumor bed is not the only cause for radiation-induced inhibition of tumor growth. (23 refs)

- 79-6907 Effect of Host Immune Capability on Radiocurability and Subsequent Transplantability of a Murine Fibrosarcoma. (Eng) Stone, H. B. (Dept. Radiology and Radia-

tion Biology, Colorado State Univ., Fort Collins, CO 80523; Peters, L. J.; Milas, L. *J Natl Cancer Inst* 63(5): 1229-1235; 1979.

The effect of host immune capability on the TCD50 (radiation dose required for local control of tumors in 50% of animals) and on the slope of the dose-response curve for tumor control in mice bearing a highly immunogenic fibrosarcoma was studied, and the transplantation kinetics of this tumor in mice whose primary tumors had been controlled by radiation were determined. Normal syngeneic C3Hf/Bu mice received the 3-methylcholanthrene-induced tumor at 9-16 wk of age. The mice were immunosuppressed temporarily by 600 rads of whole-body irradiation (WB1) or immunosuppressed permanently by thymectomy plus 900 rads of WB1 followed by reconstitution with syngeneic bone marrow (Tx1R), or were treated iv with *Corynebacterium parvum* (0.25 mg in 0.4 ml/mouse). The radiation dose necessary to achieve TCD50 was lowest (1,530 rads) in mice treated with *C. parvum* prior to irradiation. Increasing values of TCD50 were observed in normal mice, in those given 600 rads WB1 prior to tumor transplantation, and in Tx1R mice: 3,040 rads, 5,080 rads, and 6,450 rads, respectively. Considerable heterogeneity of response in normal and *C. parvum*-treated mice was observed. In many mice in which the tumor had been controlled by irradiation 4 mo previously, and in which four sc sites per mouse were injected with equal numbers of tumor cells, tumors became palpable and subsequently regressed; some mice developed tumors at all sites, while others developed no tumors. In some cases, individual mice rejected large inocula, while others could not reject small inocula. These reactions were not observed in control mice, either normal or those immunosuppressed by 600 rads WB1. (39 refs)

79-6908 Tibial Osteosarcoma Developing on a Myelomatous Focus Sterilized by Radiotherapy. (Fre) Deshayes, P. (Service de Rhumatologie, Hopital de Boisguillaume, F 76230 Boisguillaume, France); Dessauw, P.; Thorel, J. B.; Hemet, J.; Ducastelle, C.; Thomine, J. M.; Graic, Y.; Monconduit, M. *Nouv Presse Med* 8(36): 2907-2908; 1979.

A case of osteosarcoma developing in association with irradiation for myeloma of the tibia in a 25-yr-old man is described. The sternal bone marrow was normal. Light kappa chains were found in the blood and urine. Surgery was followed by telecobalt irradiation of the affected part of the tibia (total dose 3,300 rads in 11 sessions in 17 days) and by chemotherapy with melphalan (2 mg/day for 18 mo, then 30 mg on 5 consecutive days), cyclophosphamide, and vincristine (0.4 mg/day). The patient developed osteosarcoma in the irradiated area of the tibia 8 yr later. While the role of the chemotherapy cannot be ruled out, the osteosarcoma was probably induced by the irradiation. (4 refs)

79-6909 Radiation-induced Fibrosarcoma of the Mandible Following Treatment for Bilateral Retinoblastoma. (Eng) Ferlito, A. (Section Pathology, Dept. Otolaryngology, Univ. Padua, Padua, Italy); Recher, G.; Tomazzoli, L. *J Laryngol Otol* 93(10): 1015-1020; 1979.

The occurrence of a mandibular fibrosarcoma in an 11-yr-old girl treated during her first and fourth years of life for bilateral retinoblastoma is reported. The first course of treatment consisted of enucleation of the left eye followed by irradiation (total dose 3,000 rads) of the right eye and chemotherapy with vincristine and cyclophosphamide. The second course of treatment consisted of irradiation (2,000 rads) followed 3 yr later by surgery for a second

dary cataract. A poorly differentiated malignant mandibular fibrosarcoma showing extensive necrosis was diagnosed when the child was 11 yr old. She died shortly thereafter of neoplastic cachexia. It is concluded that radiation is important in carcinogenesis, but that genetic mutation may play an additional role. (11 refs)

79-6910 Local Damage and Chromosomal Changes After Exposure to Radiocobalt Source. (Cze) Klenner, V. (Institut hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia); Tuscany, R.; Novotna, J.; Sevc, J.; Thomas, J. *Prac Lek* 31(6/7): 230-234; 1979.

A ⁶⁰Co emitter with an activity of about 3 kilocuries dropped out in the course of replacement of the radiation source in the head of an irradiator at an oncological unit. The assembly technician became significantly exposed while trying to reinsert the emitter. He developed acute skin changes and focal necrosis of the left hand, the latter necessitating amputation of the fingers and part of the hand. A film dosimeter recorded the equivalent of 159 rads during the accident. The equivalent whole-body dose, estimated on the basis of chromosome analysis, was 120-160 rads. Chromosome analyses 1-28 mo post-exposure showed a decrease of the dicentric forms from 100% (0.13/cell) to 39% (0.05/cell). Deviations of dicentrics in the particular cells from Poisson's distribution confirmed the assumption of the considerable inhomogeneity of the irradiation. It is stressed that intensive sealed emitters are the most dangerous sources of accidental overexposure. (12 refs)

79-6911 Thermal Keratoses and Squamous Cell Carcinoma in Situ Associated with Erythema Ab Igne. (Eng) Arrington, J. H. (Dermatopathology Service, Moses H. Cone Memorial Hosp., 1200 N. Elm St., Greensboro, NC 27420); Lockman, D. S. *Arch Dermatol* 115(10): 1226-1228; 1979.

A 60-yr-old black woman presented with a large hyperkeratotic lesion and multiple smaller hyperkeratotic papules and plaques on the lower part of her legs in areas of erythema ab igne. Histologic examination of the largest lesion revealed hyperplastic carcinoma in situ; the multiple smaller lesions showed varying degrees of squamous cell atypia and dermal elastosis. These lesions were histologically identical to solar-induced atypia, indicating that squamous cell carcinoma arising in erythema ab igne may be biologically similar to actinic carcinoma. The patient had a history of chronic exposure to heat from sitting close to a coal fire. Clinical and histologic features of these thermal-induced lesions and other types of thermal-induced carcinomas are discussed. (20 refs)

79-6912 Carcinoma of the Hypopharynx as a Late Result of Radiation Treatment. (Ger) Glasenapp, G. B. (Hals-Nasen-Ohren-Klinik, Medizinische Akademie Magdeburg, Leipziger Strasse 44, DDR-301 Magdeburg, E. Germany); Freitag, F. *Laryngol Rhinol Otol (Stuttg)* 58(8): 629-634; 1979.

Two cases of squamous cell carcinoma of the hypopharynx in women who underwent radiation treatment for goiter during 1938-1942 are described. Severe local damage to the skin in both cases indicates that unusually large radiation dosages were given. These cases illustrate the danger of radiation treatment for benign conditions. (24 refs)

PHYSICAL CARCINOGENESIS

- 79-6913 Malignant Peritoneal Mesothelioma Following Radiotherapy for Seminoma of the Testis. (Eng) Stock, R. J. (Inst. Pathology, Case Western Reserve Univ., Cleveland, OH 44106); Fu, Y. S.; Carter, J. R. *Cancer* 44(3): 914-919; 1979.

The establishment of a diagnosis of malignant peritoneal mesothelioma is described in a 66-yr-old male patient who developed the lesion 16 yr after radiation therapy (3,200 rads) for a seminoma of the testis. The cellular similarities between mesothelioma and seminoma, as well as the patient's history, prompted a number of differing initial diagnoses. However, histochemical and ultrastructural evidence was compatible with the diagnosis of mesothelioma; the lesion was only faintly and sporadically PAS-positive, while the original seminoma was strongly PAS-positive; and ultrastructural characteristics included numerous tall microvilli on the free surfaces, tonofibrils, glycogen granules, lipid vacuoles, desmosomes, and intracytoplasmic lumens with microvilli. Historically, histologically, electron microscopically, and by microincineration, there was no evidence of asbestos exposure. The lesion may have occurred as a consequence of prior radiation therapy. (14 refs)

- 79-6914 Recovery Course in Mouse Spleen and Bone Marrow After Continuous Irradiation. (Eng) Mackova, N. (Inst. General Biology, Faculty Sciences, P.J. Safarik Univ., Moyzesova 11, CS - 041 67 Kosice, Czechoslovakia); Praslicka, M. *Folia Haematol (Leipz)* 106(3): 351-357; 1979.

The course of spleen and bone marrow recovery from irradiation was studied in adult male H strain mice continuously irradiated with a dose of 478.5 milli-Gray units (mGy: 50 R; group 1), 957 mGy (100 R; group 2), or 4,785 mGy (500 R; group 3) up to a total dose of 9,570 mGy (1,000 R) over periods of 20, 10, and 2 days, respectively. Parameters of spleen and bone marrow recovery were examined on days 0, 7, 14, 21, 28, and 60 after irradiation. Continuous irradiation caused a 55%-70% decrease in spleen wt immediately after irradiation. In group 1, spleen wt returned to control values by day 28 after irradiation, in group 2 by day 4, and in group 3 was 40% higher than that in controls by day 14. The RBC count in the spleen was decreased by 70%-90% immediately after irradiation but recovered during the postirradiation period. The cell number in the spleen was decreased to 10%-20% in all three groups. In groups 1 and 2, the cell count increased to 80%-90% that of controls on day 28, and in group 3 it was higher than that in controls. Marrow from the femur showed a dose-dependent decrease in cell count following irradiation. In groups 1 and 2, the cell count began to increase immediately after irradiation, but in group 3 it continued to decrease until day 7; it then began to increase and reached control values by day 60. These results indicate that recovery processes in the spleen and bone marrow following irradiation are completed by day 28 and 60, respectively. (19 refs)

- 79-6915 Radiation Carcinogenesis in the Syrian Hamster. (Eng) Stenback, W. A. (Div. Experimental Biology, Baylor Coll. Medicine, Houston, TX); Bryan, M. E.; Trentin, J. J. *Prog Exp Tumor Res* 23: 89-99; 1979.

Recent studies on radiation carcinogenesis in hamsters and hamster tissues are reviewed, and the authors' own studies concerning radiation carcinogenesis and the activation of endogenous viruses are presented. In the latter studies, weanling hamsters were exposed to 200-3,000 R whole-body x-irradiation in different frac-

tionated doses. Of 185 surviving animals, 13 had tumors 193-449 days after the last dose of radiation; most of these were lymphoreticular neoplasms of the spleen and liver. Ten of 11 primary tumors from animals receiving >1,500 R were positive for virus particles by electron microscopy, whereas two tumors from animals receiving lower doses were negative for virus particles. The particle count declined within two to three transplant generations after serial transplantation of virus-positive tumors. The highest tumor incidence was only 12%-13% in each of the four highest total exposure groups. The mouse has been reported to be relatively more susceptible to radiation-induced lymphomagenesis. The hamster's relative resistance may be related in part to increasing levels of relatively radioresistant, lymphomacytotoxic natural killer cells in older hamsters compared with mice. (24 refs)

- 79-6916 Circulating Blocking Factors of Lymphoid-Cell Cytotoxicity in X-Ray-induced Rat Small-Bowel Adenocarcinoma. (Eng) Stevens, R. H. (Radiation Res. Lab., 14 Medical Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA 52242); Brooks, G. P.; Osborne, J. W. *Radiat Res* 80(1): 161-169; 1979.

Circulating blocking factors capable of abrogating cell-mediated immune responses measured by in vitro lymphoid-cell cytotoxicity were identified in the sera of Holtzman outbred rats 6-9 mo after a single exposure of only the temporarily exteriorized, hypoxic ileum and jejunum to x-rays (1,700-2,000 R). These factors were found in the serum of every exposed animal regardless of whether a visibly identifiable small-bowel adenocarcinoma existed or would subsequently develop. Protection of cultured x-ray-induced rat small-bowel cancer cells from destruction by tumor-sensitized lymphoid cells, as measured by the release of lactoperoxidase-catalyzed radioiodinated membrane proteins from the tumor target cells, was conferred by the action of the blocking factors at both effector and target cell levels. The results of this study demonstrate that exposure of only the rat small intestine to ionizing radiation leads to elaboration of circulating factors which will block cell-mediated immune responses directed against cancer cells developing in the exposed tissue. (32 refs)

- 79-6917 Radiation-induced Colo-rectal Carcinoma. A Report of Seven Cases. (Eng) Moriya, Y. (Dept. Surgery, Div. Radiology, Natl. Cancer Center Hosp., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan); Koyama, Y.; Hojo, K.; Ushio, K.; Hirota, T.; Itabashi, M. *Jpn J Clin Oncol* 9(1): 153-161; 1979.

Seven patients who developed colorectal carcinoma following radiation injuries were identified among 880 patients with colorectal carcinoma seen in a Tokyo hospital between 1962 and 1978. The seven patients, six of whom were women, were initially irradiated for epidermoid carcinoma of the cervix (5 cases), epidermoid carcinoma of the vulva (1 case), or carcinoma of the cecum (1 case). The average age of the patients was 42 yr at the time of radiotherapy and 60 yr at the time of diagnosis of secondary colorectal carcinoma (latent period 16-21 yr). Six of the seven patients had metachronous double primary carcinoma and were among a total of 35 such patients in the series of 880. Four of seven radiation-induced tumors were of the localized ulcerating type, two were of the ulcerated infiltrating type, and one was of the diffuse infiltrating type. There were two poorly differentiated adenocarcinoma and two mucinous carcinomas. (14 refs)

- 79-6918 Adenocarcinoma of the Colon Following the Treatment of Wilms Tumor. (Eng) Sabio, H. (Dept. Pediatrics, Univ. Virginia Hosp., Box 386, Charlottesville, VA 22908); Teja, K.; Elkon, D.; Shaw, A. *J Pediatr* 95(3): 424-426; 1979.

The occurrence of an adenocarcinoma of the colon within a field previously irradiated for the treatment of Wilms tumor is reported. The patient, a 12-yr-old boy, had received ^{60}Co (2,100 rads over 14 days) at age 5 mo for a Group I Wilms tumor of the left kidney. Microscopic examination of the mass subsequently found in the splenic flexure of the colon revealed a poorly differentiated adenocarcinoma with areas of large amounts of mucin production. The tumor infiltrated the entire thickness of the bowel wall, was present in the pericolic fat, and had metastasized to one lymph node. The surrounding mucosa exhibited extensive radiation colitis, with areas of ulceration, inflammation, and atrophy. Focal superficial adenomatous change was noted away from the tumor in a few areas. The patient had no known history suggestive of a predisposition for early occurrence of colon carcinoma, eg, polyposis, ulcerative colitis, or a family history of malignancy. (7 refs)

- 79-6919 Cancer of the Colon on an Ileocolonic Anastomosis Prepared in 1954 for Ulcerative Hemorrhagic Rectocolitis. (Fre) Chatelin, C. L. (No affiliation given); Campora, J. L.; Fissore, A.; Fissore, O. *Ann Gastroenterol Hepatol (Paris)* 15(4): 275-276; 1979.

An ileocolonic anastomosis was established in a 25-yr-old woman with ulcerative hemorrhagic rectocolitis in 1954. The patient was in good condition for 23 yr, after which she developed recurrent diarrhea and attacks of abdominal pain. A laparotomy in 1977 revealed ulceration and adenocarcinoma of the anastomosis and ovarian, hepatic, and peritoneal metastases. (no refs)

- 79-6920 Uretersigmoidostomy Followed by Carcinoma of the Colon. (Eng) Recht, K. A. (Dept. Urology, West Virginia Univ. Medical Center, Morgantown, WV 26506); Belis, J. A.; Kandzari, S. J.; Milam, D. F. *Cancer* 44(4): 1538-1542; 1979.

Adenocarcinoma of the colon developing as a late complication of uretersigmoidostomy has been reported with increasing frequency. The case is presented of a patient who developed adenocarcinoma of the colon 28 yr after uretersigmoidostomy for bladder exstrophy and 13 yr after conversion of the uretersigmoidostomy to an ileal conduit. The colonic tumor was documented at postmortem examination to be at the uretersigmoidostomy site. Metastases to the supraclavicular lymph node were histologically identical to the primary tumor. Because of the potential late development of adenocarcinoma of the colon, careful follow-up of patients with uretersigmoidostomies, particularly those performed in childhood, is indicated. Possible mechanisms responsible for the malignant change are discussed. (28 refs)

- 79-6921 Lung Tumors from $\text{PuO}_2\text{-ZrO}_2$ Aerosol Particles in Syrian Hamsters. (Eng) Thomas, R. G. (Toxicology Group, Univ. California, Los Alamos Scientific Lab., Los Alamos, NM 87545); Smith, D. M. *Int J Cancer* 24(5): 594-599; 1979.

Syrian golden hamsters were given $\text{PuO}_2\text{-ZrO}_2$ particles via inhalation and/or Pu-laden ZrO_2 ceramic 10- μm diameter microspheres lodged in the capillary bed of the lung. The mean initial lung burdens ranged from 8 nanoCi to 143 nanoCi for the six experimental groups. Significant numbers of primary lung tumors (5%-50% of animals in each group) were induced by inhalation exposures. Additional α -radiation administered via Pu-laden iv microspheres had little or no effect on tumorigenesis or on the production of nonneoplastic, degenerative changes in the respiratory tract. (19 refs)

- 79-6922 Evaluation of Alpha Radiation-induced Respiratory Carcinogenesis in Syrian Hamsters: Total Dose and Dose-Rate. (Eng) Little, J. B. (Dept. Physiology, Harvard Univ. Sch. Public Health, Boston, MA 02115); Kennedy, A. R. *Prog Exp Tumor Res* 24: 356-369; 1979.

The induction of lung cancer in random bred male Syrian golden hamsters by multiple intratracheal instillations of ^{210}Po was studied. A dose-dependent increase in lung tumors (primarily peripheral tumors classified as combined epidermoid and adenocarcinomas) was found following irradiation of the lung with 15-15,000 rads; the tumor incidence ranged from 9% to 97%. Administration of ^{210}Po on Fe_2O_3 carrier particles resulted in a highly nonuniform distribution of the radiation dose as compared with the homogeneous distribution found following instillation of ^{210}Po in a saline solution. However, the ultimate tumor incidence was the same following administration by either method. Preliminary data indicate that dose-rate (the degree of protraction of the exposure) does not influence tumor induction by similar total radiation doses. However, the instillation procedure itself acts as a cofactor in ^{210}Po lung carcinogenesis. Hamsters appear to be highly resistant to the induction of lung cancer by inhaled α emitters as compared with rats. (30 refs)

- 79-6923 The Influence of Oxidation State on the Absorption of Plutonium from the Gastrointestinal Tract. (Eng) Sullivan, M. F. (Biology Dept., Pacific Northwest Lab., Richland, WA 99352); Ryan, J. L.; Gorham, L. S.; McFadden, K. M. *Radiat Res* 80(1): 116-121; 1979.

The effect of oxidation state on gastrointestinal absorption of plutonium was studied using solutions that either did or did not contain a strong oxidant and animals that either were or were not fasted. No appreciable differences were seen in the absorption of intragastrically injected $^{238}\text{Pu(IV)}$ (0.0003 mg) and $^{238}\text{Pu(VI)}$ (0.0005 mg) by either rats or guinea pigs on a normal diet. To determine if the conditions used in a previous study were responsible for the increased gut absorption of $^{239}\text{Pu(VI)}$, relative to $^{239}\text{Pu(IV)}$, both fasted (18 hr before until 72 hr after Pu administration) and unfasted rats were gavaged with acid soln of $^{239}\text{Pu(VI)}$ nitrate in the presence or absence of the holding oxidant ($\text{K}_2\text{Cr}_2\text{O}_7$). The results indicated that the combination of dichromate and fasting increased absorption about 26-fold. (6 refs)

- 79-6924 Role of Iron in Plutonium-239 Excretion Processes in Different Regions of the Gastrointestinal Tract. (Rus) Shvydko, N. S. (Res. Inst. Radiation Hygiene, Leningrad, USSR); Rushonik, S. I.; Popov, D. K.; Vorozhtsova, L. N. *Radiobiologiya* 19(5): 725-730; 1979.

The effect of iron on Pu239 excretion was studied in albino rats injected iv with plutonium citrate (3.0 μ Ci/mouse). The mice began receiving weekly doses of iron citrate (13.3 mg/mouse, po, 63 days) 2.5 hr after the plutonium injection. Animals were sacrificed 2.5 hr, 7, 14, 27, 42, or 63 days after isotope injection, and the gastric, duodenal, and intestinal contents were analyzed. Iron administration resulted in a two- to eightfold increase in the fraction of radionuclide absorbed by different regions of gastrointestinal tract, but did not change the rate of Pu239 elimination. (2 refs)

79-6925 Sister Chromatid Exchanges in Human Lymphocytes After Exposure to Diagnostic Ultrasound. (Eng) Liebeskind, D. (Dept. Radiology, Albert Einstein Coll. Medicine, Bronx, NY 10461); Bases, R.; Mendez, F.; Elequin, F.; Koenigsberg, M. *Science* 205(4412): 1273-1275; 1979.

The effect of ultrasound on the incidence of sister chromatid exchanges (SCE) was studied in freshly isolated human lymphocytes and in the continuously growing human lymphoblast line SKL-7.

The cells were exposed to diagnostic levels of ultrasound for 30 min between their first and second divisions (48 hr after addition of phytohemagglutinin-16 in the fresh lymphocyte culture and 18 hr after mitogen addition in the lymphoblast line). Fresh lymphocytes and the lymphoblast line showed a small but significant increase in the number of SCEs. These results suggest that ultrasound may not be entirely innocuous. (18 refs)

See also:

*(Rev.): 79-6605, 79-6621, 79-6622, 79-6623, 79-6624, 79-6625, 79-6626, 79-6627, 79-6628, 79-6629, 79-6630, 79-6631, 79-6632, 79-6639, 79-6642.

*(Chem.): 79-6657, 79-6824, 79-6825, 79-6847.

*(Immun.): 79-7076.

*(Epid.-Biom.): 79-7140, 79-7148, 79-7153, 79-7159, 79-7166, 79-7170, 79-7181.

VIRAL CARCINOGENESIS

- 79-6926 *V-15_B*, an Allele of Chickens for the Production of a Noninfectious Avian Leukosis Virus. (Eng) Robinson, H. L. (Worcester Foundation Experimental Biology, Shrewsbury, MA 01545); Astrin, S. M.; Salazar, F. H. *Virology* 99(1): 10-20; 1979.

Evidence is presented that 15_B chickens have a dominant allele *V-15_B* for the expression of a noninfectious avian leukosis virus. This virus is designated 15_B-ILV. In genetic crosses *V-15_B* cosegregated with *ev 7*, a genetic locus which contains structural genes for virus. The expression of 15_B-ILV was tightly controlled in *V-15_B* cells. The expression of other ALV germ line and infection proviruses was not infected by *V-15_B*. These results suggest that *V-15_B* consists of cis-dominant control sequences as well as structural sequences for 15_B-ILV. 15_B cells also contain a putative allele *Gr-E* which codes for high levels of replication of subgroup E viruses. In genetic crosses *V-15_B* was shown to reside at a distinct genetic locus. (31 refs)

- 79-6927 Low Frequency Production of Recombinant Subgroup E Avian Leukosis Viruses by Uninfected *V-15(B)* Chicken Cells. (Eng) Robinson, H. L. (Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545); Eisenman, R.; Senior, A.; Ripley, S. *Virology* 99(1): 21-30; 1979.

The production of subgroup E viruses by uninfected 15(B) chicken cells was studied. In contrast to the noninfectious avian leukosis virus (15B-ILV) spontaneously produced at estimated frequencies of one event per 10³ cell days by these cells, the E viruses (15B-E) were produced by 15(B) cells at an estimated frequency of one event per 2 x 10⁹ cell days. The frequency of occurrence of 15B-E viruses was affected by the level of expression of *V-15(B)*, an allele for the spontaneous production of 15B-ILV, and by the presence of endogenous viral alleles which constitutively express subgroup E envelope antigens. The proteins of nine independent isolates of 15B-E viruses were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. All isolates had p27 proteins with the distinctive mobility of the p27 of RAV-O, an endogenous virus. Each isolate also had characteristic pairs of p19 related proteins that were similar to pairs of p19 related proteins generated by recombinants of PR-RSV-C, a nondefective avian sarcoma virus, and RAV-O. Since 15B-E isolates occurred in uninfected cells and contained proteins characteristic of RAV-O and recombinants of RAV-O, it is suggested that the 15B-E viruses are recombinants of endogenous viral information. It is further suggested that 15B-ILV and RNAs which contain information for subgroup E envelope antigens are the parents of 15B-E viruses. (26 refs)

- 79-6928 Three New Types of Viral Oncogene of Cellular Origin Specific for Haematopoietic Cell Transformation. (Eng) Roussel, M. (INSERM, Oncologie Moléculaire, Institut Pasteur de Lille, 15 rue C. Guérin F 59000, Lille, France); Saule, S.; Lagrou, C.; Rommens, C.; Beug, H.; Graf, T.; Stehelin, D. *Nature* 281(5731): 452-455; 1979.

Viral oncogenes were sought in seven isolates of replication defective leukemia virus (DLV). Chicken or quail fibroblasts infected with DLV alone were used as a source of viral RNA; when hybridized with purified labeled avian leukemia virus (ALV) transcripts, 22-78% homologous material was found. Less than 3% of RNA from DLV-infected cells was bound to purified *src* gene transcripts of avian sarcoma virus (ASV). Viral clones were obtained by superinfecting nonproducer cells with plaque-purified helper virus RAV-2. When isolates were proven to be oncogenic by a bone marrow transformation test, they were propagated in chicken erythroblasts (avian erythroblastosis virus: AEV), in chicken fibroblasts (MC29), and in live chickens (avian myeloblastosis virus: AMV). Viral RNA, first hybridized to remove ALV genomes, were copied by reverse transcriptase to produce labeled DNA copies (cDNA), which could still hybridize to their corresponding RNA sources. The results showed that cDNAs prepared in this way were specific for the DLV used to produce them, that they were distinct sets of sequences unrelated to each other by cross-hybridization, and that they bore extensive homologous regions to other DLVs (cDNA of MC29 cross-hybridized with CM11, OK10, and MH2 RNA; cDNA of AMV cross-hybridized with E26 RNA). RNA of infected nonproducer cells also retained specific hybridizing properties with the appropriate cDNA of the infecting DLV. All three cDNAs were able to hybridize to DNA isolated from normal chicken DNA sequences at the rate of one or two copies per chicken genome; plateau hybridization values achieved 100%, indicating complete homology of cDNAs with normal chicken DNA. All seven DLV contained all or part of one of three unique sets of nucleotide sequences complementary to cDNA of AEV or MC29 or AMV but not to the *src* gene of ASV. Therefore, all DLV contain portions of the normal chicken genome that may code for transforming factors specific for each of the cell types that each DLV can transform. (28 refs)

- 79-6929 Chicken Hematopoietic Cells Transformed by Seven Strains of Defective Avian Leukemia Viruses Display Three Distinct Phenotypes of Differentiation. (Eng) Beug, H. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); von Kirchbach, A.; Doderlein, G.; Conscience, J. F.; Graf, T. *Cell* 18(2): 375-390; 1979.

Chicken hematopoietic cells transformed in vitro and in vivo by seven strains of replication-defective avian leukemia viruses were assayed for the expression of six erythroid and five myeloid differentiation parameters, including differentiation-specific surface antigens as detected by newly developed antisera. The transformed cells were found to display three distinct phenotypes of differentiation. First, cells transformed by AEV resembled erythroblasts. They expressed heme, globin, carbonic anhydrase and erythrocyte cell surface antigen at low levels, and histone H5 and erythroblast cell surface antigen at high levels. Second, cells transformed by MC29, CM11, OK10, and MH2 viruses had macrophage-like properties. They strongly expressed Fc receptors, phagocytic capacity, and macrophage cell surface antigen, but they only weakly ex-

pressed myeloblast cell surface antigen and were negative for adenosine triphosphatase (ATPase) activity. Third, cells transformed by AMV and E26 viruses resembled myeloblasts in that they weakly expressed Fc receptors, phagocytic capacity, and macrophage cell surface antigen but strongly expressed myeloblast cell surface antigen and ATPase activity. No difference was found between *in vitro*- and *in vivo*-transformed cells in the parameters tested. In light of recent genetic and biochemical evidence, it is concluded that these phenotypes reflect the action of three new types of viral-transforming genes, designated *erb* (erythroblast), *mac* (macrophage), and *myb* (myeloblast). (56 refs)

- 79-6930 Oligoribonucleotide Map and Protein of CMII: Detection of Conserved and Nonconserved Genetic Elements in Avian Acute Leukemia Viruses CMII, MC29, and MH2. (Eng) Bister, K. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Loliger, H. C.; Duesberg, P. H. *J Virol* 32(1): 208-219; 1979.

RNA and protein of the defective avian acute leukemia virus CMII, which causes myelocytomas in chickens, and of CMII-associated helper virus (CMIIAV) were investigated. The RNA of CMII measured 6 kilobases (kb) and that of CMIIAV measured 8.5 kb. By comparing more than 20 mapped oligonucleotides of CMII RNA with mapped and nonmapped oligonucleotides of acute leukemia viruses MC29 and MH2 and with mapped oligonucleotides of CMIIAV and other nondefective avian tumor viruses, the following three segments were distinguished in the oligonucleotide map of CMII RNA: a 5' group-specific segment of 1.5 kb which was conserved among CMII, MC29, and MH2 and also homologous with *gag*-related oligonucleotides of CMIIAV and other helper viruses; an internal segment of 2 kb conserved specifically among CMII, MC29, and MH2 and absent from an otherwise isogenic, nontransforming helper, CMIIAV; and a 3' group-specific segment of 2.5 kb which shared 13 of 14 oligonucleotides with CMIIAV and included *env* oligonucleotides of other nondefective viruses of the avian tumor virus group. This segment and analogous map segments of MC29 and MH2 were not conserved at the level of shared oligonucleotides. CMII-transformed cells contained a nonstructural, *gag* gene-related protein of 90,000 daltons, distinguished by its size from 110,000-dalton MC29 and 100,000-dalton MH2 counterparts. The *gag* relatedness and similarity to the 100,000-dalton MC29 counterpart indicated that the 90,000-dalton CMII protein is translated from the 5' and internal segments of CMII RNA. The existence of conserved 5' and internal RNA segments and conserved nonstructural protein products in CMII, MC29, and MH2 indicates that these viruses belong to a related group, termed the MC29 group. MC29 group viruses differ from one another mainly in their 3' RNA segments and in minor variations of their conserved RNA segments as well as by strain-specific size markers of their *gag*-related proteins. Because the conserved 5' *gag*-related and internal RNA segments and their *gag*-related, nonviral protein products correlate with the conserved oncogenic spectra of the MC29 group and because the internal RNA sequences and nonviral proteins are not found in nondefective viruses, it is proposed that the conserved RNA and protein elements are necessary for oncogenicity and probably are the *onc* gene and *onc* gene products of the MC29 viruses. (34 refs)

Fund, Lincoln's Inn Fields, London, England); Kitchener, G.; Graf, T. *Virology* 98(1): 191-199; 1979.

Nonproducer clones of chicken bone marrow cells and quail embryo cells transformed by avian myelocytomatosis virus strain CMII were isolated. Analysis of [³⁵S]methionine-labeled cell extracts of the nonproducer clones by immune precipitation showed that none of the three viral structural protein precursors, Pr76*gag*, gPr95^{env}, and Pr180^{gag-pol} were synthesized; instead, a 90,000 molecular wt protein (CMII-90K) was isolated. Using specific antisera, this protein was shown to be related to the *gag* gene product, but not to the products of the *pol* or *env* genes. Competition radioimmunoassays showed that nonproducer cells expressed inhibitory activity for p19 but not for p27 or p15. Tryptic peptide analysis of CMII-90K, Pr76^{gag}, gPr95^{env}, and the β -subunit of the viral reverse transcriptase confirmed the immunological data demonstrating that the CMII-90K protein contained the p19 tryptic peptides plus peptides that were specific for CMII and not related to *env* or *pol* gene products. It is concluded that the CMII-90K protein could be involved in cell transformation, especially since the tryptic peptide analysis indicated that it contains CMII-specific peptides. (39 refs)

- 79-6932 Localization of the ASV *src* Gene Product to the Plasma Membrane of Transformed Cells by Electron Microscopic Immunocytochemistry. (Eng) Willingham, M. C. (NCI, Bethesda, MD 20205); Jay, G.; Pastan, I. *Cell* 18(1): 125-134; 1979.

The cellular location of the *src* gene product (p60^{src}) of the Schmidt-Ruppin strain of avian sarcoma virus (ASV) was determined by electron microscopic immunocytochemistry in Schmidt-Ruppin ASV-transformed NRK cells, and the amount of the protein in different regions of the cell was quantified. The protein was concentrated on the inner surface of the plasma membrane, particularly under ruffles, and it was highly concentrated on the inner surface of the membrane near junctions connecting adjacent cells. Small amounts of p60^{src} were detected in the cytoplasm and in the perinuclear Golgi region of the cell. No significant localization was detected in control NRK cells or in NRK cells transformed by the Kirsten strain of murine sarcoma virus. The presence of p60^{src} on the inner surface of the plasma membrane indicates that the changes in cell growth, cell shape, and cell membrane structure noted in ASV-transformed cells are due to an initial action of p60^{src} at the cell membrane. (15 refs)

- 79-6933 Inhibition of the Transformation-specific Kinase in ASV-transformed Cells by N- α -Tosyl-L-Lysyl Chloromethyl Ketone. (Eng) Richert, N. (Div. Cancer Biology, Diagnosis, Lab. Molecular Biology, NCI, Bethesda, MD 20205); Davies, P. J.; Jay, G.; Pastan, I. *Cell* 18(2): 369-374; 1979.

The ability of N- α -tosyl-L-lysyl-chloromethyl ketone (TLCK) to inhibit the transformation-specific kinase of avian sarcoma virus (ASV)-transformed chick embryo fibroblasts (CEF) was studied. When CEF transformed with the Schmidt-Ruppin strain of ASV were treated with 0.1 mM TLCK, the kinase activity was reduced by 60% within 2 hr and by 80% after 8 hr, and it continued to remain at low levels for up to 40 hr when TLCK was present. At 24 hr after TLCK treatment, the transformed cells had reverted to a normal phenotype. When TLCK was removed, the kinase activity rose slowly over a period of several hr, the reappearance of enzyme activity corresponding with the reversion of the cells to the

- 79-6931 Cells Transformed by Avian Myelocytomatosis Virus Strain CMII Contain a 90K *gag*-related Protein. (Eng) Hayman, M. J. (Dept. Tumour Virology, Imperial Cancer Res.

transformed phenotype within 24-48 hr. The effect of TLCK *in vivo* was concentration dependent and specific. Other serine protease inhibitors had no effect on the kinase activity. At low concentrations (0.03 mM), N- α -tosyl-L-phenylalanyl chloromethyl ketone (TPCK) was partially inhibitory ($\leq 20\%$), but at higher concentrations it was extremely toxic to the CEF and could not be tested. The inhibition by TLCK was not due to its ability to inhibit protein synthesis. TLCK and TPCK, but not phenylmethylsulfonyl fluoride, inhibited kinase activity when added directly to cell extracts, but the concentrations required to produce 50% inhibition were fivefold higher than those required *in vivo*. The data suggest that kinase has an important role in transformation and offer a biochemical rationale for treatment of tumors with TLCK. (15 refs)

- 79-6934 Two Avian Sarcoma Virus Mutants with Defects in the DNA Polymerase-RNase H Complex. (Eng) Moelling, K. (Max-Planck Inst. für Molekulare Genetik, 1000 Berlin 33, W. Germany); Friis, R. R. *J Virol* 32(2): 370-378; 1979.

Two avian sarcoma virus mutants exhibiting different phenotypes were analyzed for the properties of their RNA-dependent DNA polymerase and RNase H activities. LA 338, a complex multiple mutant with at least one lesion each in transformation and replication functions, had a purified RNA-dependent DNA polymerase-RNase H complex which was twofold more thermolabile than that from the wild-type parent. The ability of the enzyme to respond to synthetic template-primers was lost more rapidly than was the response to native RNA as template. The mutant enzyme could not be protected from inactivation by the addition of synthetic template-primers. LA 672 showed a "late"-acting block in replication which affected only production of progeny by infected cells grown at the nonpermissive temperature. The purified DNA polymerase-RNase H complex of LA 672 was not thermolabile; rather, progeny grown at the nonpermissive temperature yielded purified enzyme with a 20-fold-reduced specific activity in both DNA polymerase and RNase H. Furthermore, the content of reverse transcriptase protein in such noninfectious progeny did not appear to be significantly diminished since immunologically active enzyme could be demonstrated in a competition test for anti-reverse transcriptase antibody and since β and α subunits of reverse transcriptase could be identified after polyacrylamide gel electrophoresis of partially purified enzyme preparations. The amounts of β and α from the mutant were about twofold lower. (20 refs)

- 79-6935 Immune Response to the *src* Gene Product in Mice Bearing Tumors Induced by Injection of Avian Sarcoma Virus-transformed Mouse Cells. (Eng) Parsons, S. J. (Dept. Microbiology, Univ. Virginia Medical Sch., Charlottesville, VA 22908); Riley, S. C.; Mullen, E. E.; Brock, E. J.; Benjamin, D. C.; Kuehl, W. M.; Parsons, J. T. *J Virol* 32(1): 40-46; 1979.

A single sc injection of 10^7 live cells of the highly tumorigenic avian sarcoma virus (Schmidt-Ruppin strain, subgroup D)-transformed BALB/c line into BALB/c mice resulted in the production of an antiserum specific for the avian sarcoma virus gene product pp60*src*. All sera taken from mice 3 wk after tumor cell injection contained antibodies to pp60*src*. Immunoprecipitation experiments showed that all sera precipitated pp60*src* from Schmidt-Ruppin-infected chicken cells, but only a portion of these sera precipitated pp60*src* from chicken cells infected with other strains of avian sarcoma virus (Prague and Bratislava-77). Analysis of the

cross-reactivity patterns of these antisera demonstrated a minimum of three to four antigenic determinants on pp60*src*. These findings should facilitate the production of monoclonal antibodies to pp60*src*, which in turn will provide highly specific probes for further investigations into the structure and function of this protein. (14 refs)

- 79-6936 The *src* Gene Product of Transformed and Morphologically Reverted ASV-infected Mammalian Cells. (Eng) Collett, M. S. (Dept. Pathology, Univ. Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO 80262); Brugge, J. S.; Erikson, R. L.; Lau, A. F.; Krzyzek, R. A.; Faras, A. J. *Nature* 281(5728): 195-198; 1979.

The *src* gene products in avian sarcoma virus (ASV)-transformed European field vole (*Microtus agrestis*) cells and morphologically normal revertant subclones of these cells were compared. Both the transformed and revertant cells contained the sarcoma gene product, a 60,000-mol wt phosphoprotein (pp60*src*) with an associated protein kinase activity. The *src* gene product in both transformed and revertant cells was phosphorylated to a similar extent but the pp60*src* protein in the revertant clones showed a slightly slower electrophoretic mobility than those from the transformed clones. The pp60*src* proteins present in the revertant clones may represent an altered *src* gene product since the pp60*src* proteins from transformed vole and chicken cells comigrated under the same conditions. One-dimensional peptide analyses of 35 S-methionine-labelled pp60*src* with *Staphylococcus aureus* V8 protease indicated that the pp60*src* C-terminal V8 protease peptide in the revertant cell lines had a slower electrophoretic mobility which represented a stable genetic change. No correlation could be made between the concentration of the *src* protein or the specific activity of the pp60*src* protein kinase and the transformed or morphologically reverted state of the ASV-infected cells. The results suggest that the presence of protein kinase activity in itself is not sufficient to induce morphological transformation. Since the revertant cell lines are tumorigenic, the results also indicate that one of the phenotypic parameters of cellular transformation can be expressed in the absence of another. (19 refs)

- 79-6937 Identification of a Rous Sarcoma Virus Transformation-related Protein in Normal Avian and Mammalian Cells. (Eng) Rohrschneider, L. R. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA 98104); Eisenman, R. N.; Leitch, C. R. *Proc Natl Acad Sci USA* 76(9): 4479-4483; 1979.

Immunoprecipitation with rabbit antitumor serum containing broad spectrum antibodies to a 60,000-dalton protein (pp60^{src}) product of avian sarcoma virus (ASV) was used to examine normal uninfected frog, chicken, rat, human, and *Drosophila* cells for a similar phosphoprotein. The frog, chicken, rat, and human, but not the *Drosophila*, cells contained such a protein, designated pp60. Peptide maps of [35 S]methionine-labeled pp60 and pp60^{src} indicated major similarities as well as some differences in amino acid composition, and peptide maps of 32 P-labeled proteins demonstrated that the phosphopeptides of all endogenous pp60 molecules tested were identical. However, some differences were noted between the phosphopeptide patterns of pp60 and viral pp60^{src}. The kinase activity associated with pp60^{src} was measured in the immunocomplex and resulted in the transfer of radioactive phosphorus from [γ - 32 P]ATP to the immunoglobulin heavy chain as well as to an 80,000-dalton phosphoprotein. The pp60s of

chicken, rat, and human origin also contained an associated kinase activity. These results are consistent with the notion that the pp60 molecules are the protein products of endogenous *sarc* sequences found in vertebrate cells. (28 refs)

- 79-6938 Characterization of RNA Polymerases from Rous Sarcoma Virus-induced Mouse Ascites Sarcoma Cells. (Eng) Misumi, H. (Health Lab. Okayama Prefecture, 1-1-17, Furugyo-cho, Okayama 703, Japan); Oda, T. *Acta Med Okayama* 33(2): 91-102; 1979.

RNA polymerase was extracted from the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV)-induced C3H/He mouse ascites sarcoma cells (SR-C3H) and separated into RNA polymerases I and II by DEAE-Sephadex chromatography. The main component of RNA polymerase I after phosphocellulose chromatography was 1b. Polymerase activities obtained by DEAE-Sephadex chromatography were dependent on added DNA and inhibited by RNase. The reaction was enhanced 50% by 10 mM 2-mercaptoethanol or 0.5 mM dithiothreitol. Divalent cations were required for the reaction, with the optimal concentration of Mn^{++} ions being approx 2 mM and of Mg^{++} 5-15 mM. RNA polymerase I had optimal activity at concentrations of 0.05 M ammonium sulfate $(NH_4)_2SO_4$ and RNA polymerase II at 0.1 M $(NH_4)_2SO_4$. At ionic strengths >0.2 M $(NH_4)_2SO_4$, the activities of both polymerases were strongly inhibited. At 0.05-0.1 M $(NH_4)_2SO_4$, RNA polymerase I transcribed native DNA most actively, and RNA polymerase II transcribed denatured DNA most actively. Partial digestion of DNA by DNase I enhanced RNA synthesis by RNA polymerases I and II. The initiation complexes of RNA polymerases I and II with native DNA were more stable against high salt concentration than with denatured DNA. These results suggest that the higher affinity of RNA polymerase II for denatured DNA was nonspecific or nonspecific termination of the reaction occurred. (26 refs)

- 79-6939 Relationship Between Inhibition of Protein Methylase I and Inhibition of Rouse Sarcoma Virus-induced Cell Transformation. (Eng) Enouf, J. (Institut de Chimie des Substances Naturelles, Centre National de Recherche Scientifique, 91190 Gif-sur-Yvette, France); Lawrence, F.; Tempete, C.; Robert-Gero, M.; Lederer, E. *Cancer Res* 39(11): 4497-4502; 1979.

The effects of more than 30 S-adenosylhomocysteine (SAH) analogs with modifications on the purine ring, the sugar moiety, or the 5'-side chain on protein methylase I (PMI) activity and on focus-formation in Rous sarcoma virus (RSV)-infected cells were studied in secondary cultures of chicken embryo fibroblasts. Among the compounds tested which inhibited PMI, all were competitive inhibitors with respect to S-adenosylmethionine (SAM). The analogs could be grouped into three categories: Group A, good inhibitors, containing 15 compounds all of which are modified in the 5'-side chain; Group B, medium inhibitors, containing 9 analogs with several types of chemical modifications; and Group C, poor inhibitors, containing 13 compounds. All the good inhibitors of PMI strongly prevented RSV-induced cell transformation, but the reverse was not always true. The inhibitory effect of these analogs was similar on enzymes from normal and transformed cells; no significant variation of the inhibition was observed after purification of PMI. These studies suggest a role of PMI in cell transformation. (48 refs)

- 79-6940 Relationship Between the Production of Rous Sarcoma Virus in Hamster Cells and Cell Cycle Phase. (Rus) Cherepantseva, E. A. (Lab. Virus Etiology Tumors, Inst. Epidemiology and Microbiology, Moscow, USSR); Shevliagin, V. I. *Tsitologiya* 21(10): 1189-1193; 1979.

The features of Rous sarcoma virus (RSV) production in transformed embryonal hamster cells (strain 23x) were studied. RSV production was detected only in cells in the log phase of growth; the number of infective centers on day 3 of culturing was 120/ml, compared with 4/ml on day 4, ie, during the stabilization of cell culture. Complete inhibition of cell proliferation caused by nonlethal x-irradiation (1,000 R) resulted in a decrease in or complete termination of RSV production. Blocking DNA synthesis in 23x cells caused a 10-fold decrease in RSV production. RSV production was associated with mitosis and the G1 stage of the cell cycle. (14 refs)

- 79-6941 Inhibition of Rous Sarcoma Virus Replication by 2-Deoxyglucose and Tunicamycin: Identification of an Unglycosylated *env* Gene Product. (Eng) Stohrer, R. (Dept. Microbiology, Medical Center, Univ. Alabama, Birmingham, AL 35294); Hunter, E. *J Virol* 32(2): 412-419; 1979.

2-Deoxyglucose and tunicamycin, both inhibitors of glycosylation, depressed the synthesis of infectious Rous sarcoma virus (RSV) by more than 100-fold. Under the same conditions only a two- to threefold decrease in the production of virus particles was observed. The noninfectious particles had a lower density (1.145 g/ml) in isopycnic sucrose gradients and lacked gp85 and gp37, the two virion glycoproteins found on infectious virions. The four internal structural proteins of the virus, p27, p19, p15, and p12, appeared to be assembled normally into the noninfectious virus. Polypeptides related to the RSV glycoproteins were immunoprecipitated from pulse-labeled RSV (Prague strain, subgroup B)-transformed cells. The polyprotein precursor to gp85 and gp37, pr95(gp), was the major protein precipitated from untreated cells; it was absent in both tunicamycin- and 2-deoxyglucose-treated cells, with a new polypeptide of mol wt 57,000-58,000 being the major species precipitated. This product was unstable in tunicamycin-treated cells and was degraded during a 2-hr chase; in 2-deoxyglucose-treated cells, on the other hand, the polypeptide appeared to be more stable and underwent partial glycosylation. The synthesis and processing of pr76, the polyprotein precursor to the internal structural proteins of the virion, occurred normally in both treated and untreated cells. It was concluded that the unglycosylated *env* gene product is a polypeptide of mol wt 57,000-58,000. (34 refs)

- 79-6942 Effect of Immunologic Intervention on In Vivo Murine Rous Sarcoma Virus Tumorigenesis. (Eng) Banks, R. A. (Dept. Biological Sciences, Hampton Inst., Hampton, VA 23668); Babcock, G. F.; Whitmore, A. C.; Haughton, G. *J Natl Cancer Inst* 63(6): 1423-1431; 1979.

The effect of immunologic manipulation on the development of primary murine Rous Sarcomas (PRS) was studied following the injection of Rous sarcoma virus-induced chicken tumor material (RCTM) into neonatal mice of different strains. Heterologous antithymocyte serum (ATS) treatment beginning at 7 or 21 days of age tripled and nearly doubled, respectively, the incidence of PRS, but treatment at 21 days significantly prolonged the mean latency of the tumors. Lymphoid cells from syngeneic adult mice immunized with allogeneic PRS had no effect when injected into 1-

day-old mice, but immune lymph-node cells (LNC) injected 1 wk after birth (preceded by RCTM injections on day 1 of life) significantly increased the tumor incidence. LNC and spleen cells (SC) from syngeneic adult mice that had been inoculated with RCTM at birth but had developed tumors by 200 days of age (VT) decreased tumor incidence when administered on day 1 but not on day 7. Normal adult SC and LNC had no effect when given on day 1 but significantly increased tumor incidence when given on day 7. Serum from adult immune, VT, and tumor-positive mice decreased the PRT incidence when given on days 1 and 7. The offspring of immune mothers were less susceptible than those of normal mothers. The offspring of passively immunized mothers given serum from immune females during pregnancy were more susceptible than controls. RCTM-inoculated mice appeared to be susceptible only to immunologic manipulations that reduced PRT incidence during the first few days of life. (32 refs)

- 79-6943 Analysis of the *src* Gene of Sarcoma Viruses Generated by Recombination Between Transformation-defective Mutants and Quail Cellular Sequences. (Eng) Wang, L. H. (Rockefeller Univ., New York, NY 10021); Moscovici, C.; Karess, R. W.; Hanafusa, H. *J Virol* 32(2): 546-556; 1979.

Inoculation of a transformation-defective (td) mutant of Schmidt-Ruppin strain Rous sarcoma virus strain A (SR-A) that retained a small portion of the *src* gene induced tumors in quails after about 1 mo. A td mutant with nearly complete deletion of the *src* gene did not induce tumors. The avian sarcoma viruses recovered from 5/5 quail tumors (rASV-Q) were biologically similar to the viruses (rASV-C) isolated from chicken tumors induced by the same td mutants. Both rASV-Q and rASV-C transformed cells in culture with similar focus morphology, and induced tumors 7-14 days after inoculation into chickens or quails. The sequences of rASV-Q RNA genomes were compared to those of the parental td virus (SR-A) and rASV-C. All five rASV-Q isolates had identical *src* sequences, which differed from those of SR-A and rASV-C. Two of 13 *src*-specific oligonucleotides found in rASV-Q were not found in either SR-A or rASV-C RNA. The *src* regions of SR-A and/or rASV-C RNA's also contained some oligonucleotides which were not found in rASV-Q. There were no differences in sequences outside the *src* region in any of these viruses. The rASV-Q-infected cells also had a 60,000-dalton protein, which was specifically precipitable by rabbit serum against SR-D-induced tumors. The facts that *src* sequences were essentially the same for rASV's from one species of bird and different for rASV's obtained from another species provide conclusive evidence that cellular sequences from normal host tissues were inserted into the viral genome, supplying to the resulting recombinant viruses the genetic information for cell transformation. (33 refs)

- 79-6944 Circular Forms of DNA Synthesized by Rous Sarcoma Virus In Vitro. (Eng) Clayman, C. H. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Mosharrafa, E. T.; Anderson, D. L.; Faras, A. J. *Science* 206(4418): 582-584; 1979.

The presence of circular mature forms of retrovirus DNA was demonstrated by electron microscopic analysis of the DNA product synthesized by detergent-disrupted preparations of Rous sarcoma virus in vitro. The identification of such circular DNA indicates that virions of retroviruses contain all the components necessary to facilitate the complete synthesis of mature forms of

viral DNA and therefore provide a useful system to delineate the molecular mechanisms involved in their synthesis. (14 refs)

- 79-6945 Viral Transformation of Chick Myogenic Cells. The Relationship Between Differentiation and the Expression of the SRC Gene. (Eng) Moss, P. S. (Dept. Zoology, Univ. California, Berkeley, CA 94720); Honeycutt, N.; Pawson, T.; Martin, G. S. *Exp Cell Res* 123(1): 95-105; 1979.

Chick embryo presumptive muscle cells transformed at 35 C with a temperature-sensitive mutant of Rous sarcoma virus, tsLA29, do not undergo myogenic differentiation but revert to a phenotypically normal state and fuse into myotubes when shifted to 41 C. Studies of this phenomenon revealed the activation of myosin synthesis, the appearance of myosin messenger RNA active in vitro, and acetylcholinesterase (AChE) synthesis following a shift from 35 C to 41 C. The activation of myosin synthesis also occurred in cultures prevented from fusing by calcium deprivation. However, after myosin synthesis had been initiated at 41 C, it could not be suppressed by shifting the cultures back to 35 C. [³H]Thymidine labeling and autoradiography demonstrated that DNA synthesis in tsLA29-infected myoblasts ceased within 24 hr after the shift to 41 C. A kinetic analysis of the withdrawal of these cells from the cell cycle indicated that at least a fraction of the cells do not need to traverse a complete cell cycle prior to terminal differentiation. (51 refs)

- 79-6946 The Influence of Host Adaptation of Rous Sarcoma Virus on the Transfecting Activity of its DNA Provirus. (Eng) Hlozanek, I. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 166 10 Prague 6, Czechoslovakia); Svoboda, J.; Dostalova, V.; Mach, O. *J Gen Virol* 45(1): 139-147; 1979.

In previous studies, mammalian cells transformed with either Prague strain Rous sarcoma virus of subgroup C (XC cells) or Schmidt-Ruppin strain Rous sarcoma virus of subgroup D (RSCH cells) yielded virus upon fusion with chick cells. Virus was also rescued by transfection of DNA from these cells onto chick cells. However, virus rescue did not occur upon transfection of duck cells, and fusion with duck cells led to virus rescue only from RSCH and not from XC cells. In the present study this restriction on duck cells was investigated. The nondefective Prague strain of Rous sarcoma virus of subgroup C (PR-RSV-C) was adapted for efficient replication in duck embryo cells (daPR-RSV-C) by long-term passage in vitro. However, a second PR-RSV-C isolate, rescued from the rat XC sarcoma line (XC DNA 940 virus), failed to adapt to growth in duck cells. When transformed with daPR-RSV-C, which replicates in duck cells as well as in brown leghorn embryo (BLEF) cells, duck cells yielded DNA that transfects fresh duck cells, in contrast to DNA isolated from chicken or duck cells transformed with parental PR-RSV-C. (31 refs)

- 79-6947 Selective Replication of Transformation-defective Avian Sarcoma Virus Mutants in Duck Embryo Fibroblasts. (Eng) Shimakage, M. I. (Dept. Tumor Viruses, Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita City, Osaka, Japan); Kamahora, T.; Hakura, A.; Toyoshima, K. *J Gen Virol* 45(1): 99-105; 1979.

VIRAL CARCINOGENESIS

Differences in the replicating capacity of sarcoma viruses and their transformation-defective (*td*) mutants are described. When an avian sarcoma virus (ASV), subgroup C Bratislava 77 (B77-C), was inoculated into duck embryo fibroblast cultures (DEF) at a multiplicity of infection (moi) of 0.02, its replication was retarded by about 3 days compared with that in chick embryo fibroblast cultures (CEF). A *td* mutant was isolated during this period of retardation. Unlike the sarcoma virus, this *td* mutant replicated in both DEF and CEF with no retardation, even at a low moi. The subgroup C Prague strain of Rous sarcoma virus (PR-C), which can infect DEF, also replicated in DEF slower than its *td* mutant, *td*PR-C, at a moi of 0.02. (20 refs)

- 79-6948 Tryptic Peptide Analysis of Avian Oncovirus *gag* and *pol* Gene Products. (Eng) Rettenmier, C. W. (Rockefeller Univ., New York, NY 10021); Karess, R. E.; Anderson, S. M.; Hanafusa, H. *J Virol* 32(1): 102-113; 1979.

Radiolabeled tryptic peptides of the *gag* and *pol* gene products of avian oncoviruses [Rous-associated virus 2 structural proteins and the Pr76(*gag*) and P180(*gag-pol*) proteins] were examined in Rous-associated virus 2-infected chicken embryo cells. The methionine- and cysteine-containing tryptic peptides of virion internal structural proteins were present in both Pr76(*gag*) and P180(*gag-pol*), suggesting that there was no loss of *gag* gene-coding sequences during the generation of P180(*gag-pol*). No overlap of *gag* and *pol* gene structural information was detected. Analysis of intermediates in the processing of Pr76(*gag*) and translation inhibition mapping with pactamycin yielded the following order of structural proteins within the Rous-associated virus 2 Pr76(*gag*) precursor: NH₂-p19-p12-p27-p15-COOH. The *gag* and *pol* sequences missing in the endogenous gs⁺ P120 protein of uninfected gs⁺ chicken cells were identified by comparison with those of Rous-associated virus 2 P180(*gag-pol*). (29 refs)

- 79-6949 Cell Fusion for Genetic Analysis of Two Nonconditional Rous Sarcoma Virus Replication Mutants. (Eng) Steimer, K. S. (Dept. Surgery, Children's Hosp. Medical Center, Boston, MA 02115); Boettiger, D. *J Virol* 32(1): 175-186; 1979.

Procedures for characterizing replication-defective viruses in nonpermissive mammalian cells were developed and applied to three nonvirogenic Rous sarcoma virus (RSV)-transformed mammalian cell lines: B4, a line of Bryan virus-transformed hamster cells; and two Schmidt-Ruppin D virus-RSV transformed rat cell lines, LR3/1 and LR3/2. Cell fusion was used to study virus complementation. The three cell lines fused with helper virus-infected chicken cells and the host range of the rescued virus examined, tested for complementation by fusion with chicken cells exhibiting various patterns of endogenous virus expression, fused with chicken cells infected with the temperature-sensitive replication mutant LA334 and assayed for complementation of permissive and nonpermissive temperatures, and tested for complementation of defective viruses in other RSV-transformed mammalian cell lines by fusing pairs of nonvirogenic cell lines and permissive chicken cells. Based upon these complementation studies, it was concluded that B4 virus is defective only in the *env* gene, LR3/1 virus is an absolute mutant in the *gag* and/or *pol* genes, and LR3/2 virus is a leaky *env* mutant. Clones of LR3/1 and LR3/2 virus-infected chicken cells were established, and the results obtained from the characterization of these viruses in permissive avian cells substantiated the conclusions reached in the fusion-rescue studies. (50 refs)

- 79-6950 Relationship Between Rous Sarcoma Virus-induced Expression of Membrane Antigen and Phenotypic Transformation. (Eng) Comoglio, P. M. (Istituto di Anatomia Umana Normale, Univ. Torino, Corso Massimo d'Azeglio, 52, 10126 Turin, Italy); Pani, B.; Prat, M.; Tarone, G.; Montibragadin, C. *Cancer Res* 39(11): 4744-4748; 1979.

Rous sarcoma virus-transformed hamster BHK fibroblasts express a virus-induced cell surface antigen not detectable in cells either transformed by unrelated viruses or infected by transformation-defective strains of Rous sarcoma virus. To clarify whether this antigen plays any role in the process of malignant transformation or is expressed at the cell surface only as a consequence of the acquisition of the transformed phenotype, antigen expression at the cell surface was investigated in Rous sarcoma virus-transformed BHK cells treated with dibutyl cyclic adenosine 3':5'-monophosphate (dibutyl cAMP) and in parental BHK cells transiently transformed by the tumor promoter phorbol myristate acetate (PMA). In the dibutyl cAMP-monophosphate-treated cells, most of the parameters of the transformed phenotype were reverted to normality while the product of the transforming gene was still present, and virus-induced cell surface antigen was expressed. In the mirror experiment, this antigen was not expressed by phenotypically transformed but genetically normal PMA-treated cells. It was concluded that the tumor membrane antigen studied is intimately associated with the expression of the function(s) controlled by the transforming gene. (33 refs)

- 79-6951 Failure to Confirm Evidence for a Nonviral Tumor-specific Surface Antigen in Avian Retrovirus-transformed Cells. (Eng) Phillips, E. R. (Dept. Pathology, Queen's Univ., Kingston, Ontario K7L 3N6, Canada); Perdue, J. F. *J Natl Cancer Inst* 63(4): 991-994; 1979.

Triton X-100 or Nonidet P40-deoxycholate extracts of [³H]fucose-labeled Rous sarcoma virus-transformed chick embryo fibroblasts were examined by indirect immunoprecipitation for the presence of a tumor-specific neoantigen of 100,000 daltons. Extracts were incubated with immune IgG from Rous tumor-sensitized chickens, and the resultant antigen-antibody complexes were precipitated with rabbit anti-chicken IgG and analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Radioactivity appeared between the migration positions of proteins having mol wts of 65,000 and 95,000 daltons and at about 30,000 daltons. These antigens were group-specific, and their precipitation was inhibited by competition with extracts from cultured fibroblasts that had been infected with a nontransforming avian leukosis virus. They were not precipitated with IgG from unimmunized chickens or chickens immunized with the culture supernatants of uninfected chick embryo fibroblasts. In contrast to recently reported results, the present results did not confirm the existence of a tumor neoantigen different from that associated with viral components. However, the tumor-specific antigen may have existed on the cell surface but was not preserved in these detergent extracts. (22 refs)

- 79-6952 Cellular and Humoral Immune Reactivity to Tumor-associated Antigens in Chickens Infected with Rous Sarcoma Virus. (Eng) Hall, M. R. (Dept. Microbiology, Mayo Clinic, Rochester, MN 55901); Qualtiere, L. F.; Meyers, P. *J Immunol* 123(3): 1097-1105; 1979.

The time course of the development of cellular reactivity to Rous sarcoma virus (RSV) tumor-associated antigens over time was

determined using a leukocyte blastogenesis assay. WBC reactivity to mitogens in RSV-injected birds was also investigated. Cellular immunity to 3 M KCl extracts of avian tumor virus (ATV)-infected chick embryo fibroblasts (CEF), principally to those extracts containing structural components of the virus envelope, developed 3-5 wk after injection (during tumor growth and regression) and then declined, although the immune response could be restimulated by virus rechallenge. Responses to nonviral tumor-specific surface antigen (TSSA) were weak except after RSV rechallenge. There were no differences in phytohemagglutinin (PHA) responsiveness between the WBC of RSV-injected birds and control birds, but responses to pokeweed mitogen (PWM) were sometimes elevated in RSV-injected animals. Humoral reactivity as measured by an isotopic antiglobulin test (IAT) also seemed to correlate well with the presence of virus envelope antigens (VEA) on infected indicator cells and appeared before antiviral neutralizing antibody. These data show that during the primary response, major immune reactivity in RSV-injected birds is directed against VEA and that TSSA is most immunogenic when VEA is also present. (54 refs)

- 79-6953 Deletion Mutant of the Bratislava-77 Strain of Rous Sarcoma Virus Containing a Fusion of the Group-specific Antigen and Envelope Genes. (Eng) Dierks, P. M. (Dept. Microbiology, Institut für Molekularbiologie I, Universität Zürich, Honggerberg, 8093 Zürich, Switzerland); Highfield, P. E.; Parsons, J. T. *J Virol* 32(2): 567-582; 1979.

A deletion mutant of the Bratislava-77 strain of Rous sarcoma virus (B77-RSV) containing a large deletion (3,500 nucleotides) in the polymerase region of the viral genome was detected and characterized. The deletion mutant accumulated after multiple passages of B77-RSV on Peking duck embryo fibroblasts. In each of two independently passaged B77 stocks, >77% of the viral subunits contained the deletion after 7-8 passages. It was determined, by ribonuclease T1-resistant oligonucleotide fingerprint analysis of viral RNA, direct RNA sequencing, and analysis of virus-specific proteins synthesized in vivo and in vitro, that the deletion encompasses the 3' terminus (approx 250 nucleotides) of the *gag* gene, all of the *pol* gene, and some (probably <500 nucleotides) of the *env* gene. (42 refs)

- 79-6954 Evidence for the Identity of Shared 5'-Terminal Sequences Between Genome RNA and Subgenomic mRNA's of B77 Avian Sarcoma Virus. (Eng) Stoltzfus, C. M. (Dept. Microbiology, Univ. Iowa, Iowa City, IA 52242); Kuhnert, L. K. *J Virol* 32(2): 536-545; 1979.

The polyribosomal fraction from chicken embryo fibroblasts infected with B77 avian sarcoma virus contained 38S, 28S, and 21S virus-specific RNA's, in which sequences identical to the 5'-terminal sequence (101 bases) of the 38S genome RNA were present. The only polyadenylic acid-containing RNA with 5' sequences which was detected in purified virions had a sedimentation coefficient of 38S. The findings are consistent with the hypothesis that a leader sequence derived from the 5' terminus of RNA is spliced to the bodies of the 28S and 21S messenger RNA's (mRNA's), both of which are derived from the 3' terminal half of 38S RNA. Several experiments showed that the majority of the subgenomic, intracellular virus-specific mRNA's contained the entire 101-base 5'-terminal sequence of the 38S genome RNA. In addition, a small population of virus-specific RNA's contained either a shortened 5' leader sequence or additional splicing in the terminal 101 bases. (32 refs)

- 79-6955 Transfer of Natural Resistance to Marek's Disease (JMV) with Non-Immune Spleen Cells. I. Studies of Cell Population Transferring Resistance. (Eng) Lam, K. M. (Dept. Microbiology, Sch. Veterinary Medicine, Tuskegee Inst., Tuskegee, AL 36088); Linna, T. J. *Int J Cancer* 24(5): 662-667; 1979.

The mechanism of age-related resistance to the JMV line of Marek's disease virus (MDV) was studied using SC chickens. Seven-wk-old birds were significantly more resistant to ip JMV cell challenge than were newly hatched chicks ($p < 0.002$). Chickens receiving 5×10^7 normal spleen cells from untreated 8-wk-old donors also showed significantly lower mortality from tumors than those not receiving spleen cells ($p < 0.002$). Spleen cells from thymectomized and sham-thymectomized birds were equally effective in this respect, and spleen cells treated with anti-T serum and complement were able to protect newly hatched chicks from JMV malignancy. Significant protection was also afforded by spleen cells from bursectomized donors and donors depleted of both the T- and B-cell populations. Significant protection was given by spleen cells from which both phagocytic and adherent cells had been removed ($p = 0.002$). Thus, the cell transferring resistance does not appear to belong to the major T-cell, B-cell, or macrophage populations but instead seems to be part of the functionally heterogeneous 'third cell' population. (23 refs)

- 79-6956 Pheasant Virus DNA Polymerase is Related to Avian Leukosis Virus DNA Polymerase at the Active Site. (Eng) Bauer, G. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Temin, H. M. *J Virol* 32(1): 78-90; 1979.

The DNA polymerase from Amherst pheasant virus (APV), a member of the pheasant virus species of retroviruses, was compared to the DNA polymerases of avian leukosis viruses (ALV) and a reticuloendotheliosis virus (spleen necrosis virus; SNV). Immunoglobulin inhibition tests and competition immunoassays showed that APV and ALV DNA polymerases are closely related at their active sites. The determinants common to their active sites are not shared by SNV DNA polymerase. In a species-specific radioimmunoassay, both APV and SNV DNA polymerases were grossly different from ALV DNA polymerase. The specificity of the relationship of the active sites of APV and ALV DNA polymerases was confirmed by a heterologous radioimmunoassay. These data indicate that pheasant viruses are evolutionarily linked to ALV. (21 refs)

- 79-6957 Detection of Polymorphism in BALB/c Leukemia Viruses with Mouse Antisera. (Eng) Brown, J. P. (Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Boiuchi, M.; Nowinski, R. C. *J Virol* 32(1): 345-349; 1979.

Three murine antisera, which recognize primarily type-specific antigenic determinants on both the major core protein, p30, and the major envelope proteins, gp70 and p15(E), of BALB/c endogenous murine leukemia viruses (MuLV), were investigated in detail. Antisera prepared in C57BL/6 mice against the AKR leukemia K36 reacted with the gp70, p15(E), and p30 proteins of MuLV. Certain pools of the C57BL/6 anti-AKR K36 serum contained antibodies which serologically distinguished the p30 proteins of N-ecotropic, B-ecotropic, and xenotropic BALB/c MuLV. Antisera prepared in BALB/c mice against the BALB/c sarcoma 1315 contained antibodies that reacted with a type-specific antigen of the 1315 MuLV gp70 that is not found on other BALB/c

MuLV. The normal sera of multiparous BALB/c mice contained antibodies that reacted with gp70 and p15(E) proteins of ecotropic MuLV. Sera from some of these mice contained antibodies that serologically distinguished the gp70 of N-ecotropic and B-ecotropic BALB/c viruses. These results emphasize the utility of mouse antisera in the serological typing of MuLV. Furthermore, the antigenic differences observed in the p30 and gp70 proteins should be of particular use in the future analysis of recombinant BALB/c MuLV. (30 refs)

- 79-6958 Polymorphism of B-Tropic Leukemia Viruses from BALB/c Mice: Association of a p30 Antigen with N-Versus B-Tropism. (Eng) Tress, E. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); O'Donnell, P. V.; Camulari, N.; Ellis, R. W.; Fleissner, E. *J Virol* 32(1): 350-355; 1979.

Comparison of a number of murine leukemia virus clones by sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed extensive protein polymorphism among B-tropic, but not N-tropic, isolates from BALB/c mice, particularly in migration of p30 proteins. A type-specific radioimmunoassay for p30 was developed which uniformly discriminated all B-tropic viruses from N-tropic viruses of BALB/c origin. N- and B-tropic viruses of C57BL/6 and AKR *Fv-1(b/b)* origin could also be distinguished by this assay. (37 refs)

- 79-6959 Monoclonal Antibodies Against Murine Leukemia Viruses: Identification of Six Antigenic Determinants on the p15(E) and gp70 Envelope Proteins. (Eng) Lofstrom, M. E. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA 98104); Stone, M. R.; Tam, M.; Burnette, W. N.; Pinter, A.; Nowinski, R. C. *Virology* 98(2): 336-350; 1979.

Twenty-three independently derived hybrid cell lines that produced monoclonal antibodies against the envelope proteins of murine leukemia virus (MuLV) were characterized. These hybrid cells were prepared by the polyethylene glycol-mediated fusion of a mouse myeloma cell line with lymphocytes from mice immunized with allogeneic MuLV-producing leukemia cells. The 23 cell lines were cloned and inoculated into syngeneic mice for the production of ascites fluids that contained high-titered (20-75 mg/ml) monoclonal antibodies. Six serologically distinct specificities were detected when these ascites fluids were tested on a broad panel of MuLV and non-murine retroviruses. Prototype cell lines producing monoclonal antibodies representative of each pattern of reaction were selected for further study. In immune precipitation assays, each prototype antibody reacted with viral envelope proteins; three of these identified antigenic determinants on p15(E), while three others identified antigenic determinants on gp70. The p15(E) antigenic determinants were shared by a diverse panel of MuLV. One of these p15(E) antigenic determinants was also found in feline leukemia virus. The gp70 antigenic determinants, on the other hand, had a more restricted distribution and were found in only selected isolates of MuLV. (26 refs)

- 79-6960 Suppression of the Immune Response in Tumor-bearing Mice. I. Response to Virus-producing Tumor Cells and Non-Virus-producing Tumor Cells. (Eng) Bluestone, J. A. (Lab. Herpes Virus Infections, Memorial Sloan-Kettering

Cancer Center, 1275 York Ave., New York, NY 10021); Lopez, C. *J Natl Cancer Inst* 63(5): 1215-1220; 1979.

To determine the tumor antigen(s) responsible for inducing suppressor cells and to study the cell interactions leading to the suppression of the cell-mediated immune response, suppression induced by virus-producing and -nonproducing syngeneic tumors was investigated. In addition, athymic nude mice inoculated with syngeneic tumor cells were studied. Spleen cells from mice inoculated with syngeneic murine sarcoma virus (MuSV)-transformed tumor cells demonstrated a depressed response in the mixed leukocyte reaction. Mice inoculated with virus-producing tumor cells demonstrated two types of suppression. First, an early suppression was shown to be mediated by an adherent suppressor T-cell on the basis of its sensitivity to Thy 1.2 antiserum plus complement and the absence of the early suppression in T-cell-deficient nude mice. This suppression may have been induced in response to viral antigens associated with cell surface antigens (modified self-antigens) or viremia, because it was not induced by a non-virus-producing tumor cell line. Second, late suppression was shown to be T-cell-independent by its presence in nude mice and by its resistance to γ -irradiation and Thy 1.2 antiserum plus complement. In addition, late suppression was present in mice inoculated with a nonproducer clone of MuSV-transformed cells. This finding suggests that viral antigens and/or viremia is not required for the induction of late suppression. (26 refs)

- 79-6961 Organization of Mouse Mammary Tumor Virus-specific DNA Endogenous to BALB/c Mice. (Eng) Cohen, J. C. (Dept. Microbiology and Immunology, Tulane Univ. Sch. Medicine, New Orleans, LA 70112); Majors, J. E.; Varmus, H. E. *J Virol* 32(2): 483-496; 1979.

Restriction endonucleases were used to prepare physical maps of the mouse mammary tumor virus (MMTV)-specific DNA endogenous to the BALB/c mouse strain. The mapping was facilitated by the DNA transfer procedure, using complementary DNAs specific for the whole and for the 3' terminus of MMTV RNA to detect fragments containing viral sequences. Arrangement of the fragments into physical maps was accomplished through sequential digestions with two or three enzymes, preparative isolation of *EcoRI* fragments containing viral sequences, and comparisons of virus-specific fragments derived from the DNA of several mouse strains. It was found that most of the MMTV-related DNA in the BALB/c genome is organized into two units (II and III) which strongly resemble proviruses acquired upon horizontal infection with milk-borne strains of MMTV and other retroviruses. These units contain approx 6.0×10^6 M(r) of apparently uninterrupted viral sequences; they bear redundant sequences totaling at least 700 to 800 base pairs at their termini, and these include sequences derived from the 3' end of MMTV RNA. Units II and III are closely related in that they share 12 of 14 recognition sites for endonucleases, but cellular sequences flanking units II and III are dissimilar by this criterion. The remainder of the MMTV-related DNA endogenous to BALB/c mice is found in a single unit (unit I) with a complexity of approx 2×10^6 M(r); the structure of unit I was not further defined. These results support the hypothesis that endogenous proviruses have been acquired by infection of germinal tissues with MMTV. The physical maps can be used in studies of the natural history of mammary tumorigenesis to identify the MMTV genomes endogenous to BALB/c mice. (37 refs)

- 79-6962 In Vivo and In Vitro Phosphorylation of Murine Mammary Tumour Virus Proteins. (Eng) Dion, A. S.

(Dept. Molecular Biology, Inst. Medical Res., Copewood Street, Camden, NY 08103); Fout, G. S.; Pomenti, A. A. *J Gen Virol* 44(3): 669-678; 1979.

In vitro and in vivo phosphorylation of murine mammary tumor virus (MMTV), a type B RNA virus, were compared. The protein kinase activity associated with MMTV catalyzed in vitro phosphorylation of endogenous virus polypeptides. This kinase activity required a divalent metal cation, a nonionic detergent, and was stimulated in the presence of dithiothreitol. Exogenous cyclic AMP was not required. The ^{32}P -labeled products of the in vitro reaction were completely sensitive to pronase digestion, and the phosphate was attached mainly by phosphomonoester linkage to serine residues. As determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, heterogeneous labeling of major and minor virus polypeptides was observed under in vitro conditions. In contrast, the in vivo labeling of type B virus produced by a continuous cell line (MuMT-73), established from pooled mammary adenocarcinomas of Balb/c \times C $_3$ H mice, demonstrated specific phosphoproteins associated with MMTV. The major phosphorylated proteins were found to have mol wt 18,000 and 12,000 (p18 and p12) after isolation by molecule sieving chromatography and analysis by gel electrophoresis. (24 refs)

79-6963 Hormonal Regulation of Murine Mammary Tumor Virus RNA Expression During Mammary Tumorigenesis in BALB/c Mice. (Eng) Pauley, R. J. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX 77030); Medina, D.; Socher, S. H. *J Virol* 32(2): 557-566; 1979.

The effects of glucocorticoids and prolactin on murine mammary tumor virus (MuMTV) RNA expression were investigated in preneoplastic outgrowth lines and mammary tumors in BALB/c mice. Hyperplastic alveolar nodules (HAN) and a ductal hyperplasia (DH) were induced in virgin BALB/c mice by prolonged hormonal stimulation, treatment with 7,12-dimethylbenz(a)anthracene (DMBA), or a combination of the two. Mice bearing HAN or DH outgrowth lines and mammary tumors arising from them were treated with glucocorticoids or prolactin, and MuMTV RNA was quantitated by hybridization with a representative complementary DNA probe specific for MuMTV RNA. Prolactin treatment did not increase MuMTV RNA in the BALB/c HAN or DH outgrowth lines or tumors. MuMTV RNA increased after glucocorticoid treatment in the C3, C4, and C5 HAN outgrowth lines (derived from DMBA-induced HAN) and in tumors that arose from the D1 and D2 (derived from hormonally induced HAN), the C4 and C5, and the CD8 DH (derived from DMBA-induced DH) outgrowth lines. No increase in MuMTV RNA with glucocorticoid treatment was observed in the D1 or D2 HAN outgrowth lines, in the CD8 DH outgrowth line, and in tumors that arose from the C3 HAN outgrowth line. The ability of glucocorticoids to stimulate MuMTV expression was specific, as indicated by the dose dependence and hormone specificity of the response. Glucocorticoid treatment did not increase the level of type C viral RNA in the majority of hormone- or DMBA-induced HAN outgrowth lines or tumors. These observations suggest that glucocorticoids may influence MuMTV expression during mammary tumorigenesis in BALB/c mice. (39 refs)

79-6964 Polyprotein Precursors to Mouse Mammary Tumor Virus Proteins. (Eng) Anderson, S. J. (Dept. Biology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and

Tumor Inst., Houston, TX 77030); Naso, R. B.; Davis, J.; Bowen, J. M. *J Virol* 32(2): 507-516; 1979.

Seven proteins, ranging in mol wt from 10,000 to 55,000 daltons (gp55, gp33, p25, pp20, p16, p12, and p10), were identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis of mouse mammary tumor viruses (MMTV) obtained from the culture medium of GR mouse mammary adenocarcinoma cells. Each of these proteins contained methionine and leucine. The major viral phosphoprotein was pp20. Immunoprecipitation studies showed that gp55 and gp33 arise from a common precursor (gPr76env). The MMTV glycoproteins and gPr76env could be labeled with radioactive leucine and glucosamine; labelling with fucose indicated that synthesis of gp33 and gp55 may involve a minor, high-mol wt, and heavily fucosylated polyprotein (gPr79env). A 78,000-dalton protein doublet (Pr78gag) had antigenic determinants in common with at least p25 and p12. Tryptic mapping confirmed the precursor-product relationship of Pr78gag and p25 and indicated that Pr78gag shares peptides with p12 and p10. The results of chase experiments indicated that gPr76env has a more rapid turnover than Pr78gag in cultured GR cells; labeled gp55 was formed (presumably from the cleavage of gPr76env or gPr79env, or both), but no significant amounts of p25 or other gag proteins were observed, even though Pr78gag appeared to chase and viral particles appeared in the chase medium. These results may indicate the existence of an efficient precursor processing, or may reflect the precursor product relationship between the A and B particles of MMTV. The low levels of p25 in infected cells suggest that maturation occurs coincidentally with budding of the virus. (40 refs)

79-6965 Impaired Maturation of Mouse Mammary Tumor Virus Precursor Polypeptides in Lymphoid Leukemia Cells, Producing Intracytoplasmic A Particles and No Extracellular B-Type Virions. (Eng) Nusse, R. (Dept. Virology, Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands); van der Ploeg, L.; van Duijn, L.; Michalides, R.; Hilgers, J. *J Virol* 32(1): 251-258; 1979.

Processing of mouse mammary tumor virus polypeptides was investigated in a transplanted thymic lymphoma cell line of the GR strain (GRSL) maintained in vivo in ascites form and in vitro as a suspension culture. GRSL cells produce clusters of intracytoplasmic A particles and are virtually deficient in the production of mature extracellular B-type particles. As control, a mammary tumor cell line of the same mouse strain capable of complete virion synthesis was used. The kinetics of viral polypeptide synthesis were studied by pulse labeling with various isotopes (including ^{35}S and ^{32}P), followed by immunoprecipitation of cell lysates with monospecific antisera to the major mouse mammary tumor virus gag and env proteins, p27 and gp52, respectively. Both the primary gag and env precursor polypeptides were synthesized in the GRSL cells, but their conversion into viral proteins was impaired. The major gag precursor, Pr73(gag), was stable over a period of 8 hr; and mature viral core polypeptides could not be detected. Also, the highly phosphorylated intermediates in the proteolytic processing of Pr73(gag) in virus-producing cells were absent in GRSL cells. By immunoprecipitation, Pr73(gag) was detected in a GRSL particle fraction with the density of intracytoplasmic A particles. The precursor for envelope proteins, Pr73(env), was turned over without the generation of mature viral envelope components gp52 and gp36. The in vivo-transplanted ascites GRSL cells, however, expressed gp52 on the cell surface together with a 73,000-dalton polypeptide, as indicated by cell surface iodination and immunoprecipitation. (30 refs)

VIRAL CARCINOGENESIS

- 79-6966 Cultivation of Mouse Mammary Tumor Cells Derived from DD/Tbr. II. Characteristics of MuMTV-producing Cell Lines. (Eng) Iwai, M. (Dept. Parasitology, Nara Medical Univ., Nara, Japan); Iwai, Y.; Takamori, Y.; Okumoto, M.; Murata, Y. *Annu Rep Radiat Cent Osaka Pref* 19: 95-100; 1978.
- Three clonal sublines isolated from the established cell line DDMT-761, derived from a spontaneous mammary tumor in a DD/Tbr mouse, were designated DDMT-762, -763, and -764. Cell lines 762 and 763 were epithelioid, and their growth properties were similar to those of the parental cell line. Cell line 764 was fibroblastic and was the fastest-growing of the four cell lines. The epithelial cell lines could be maintained for 2 mo or more by changing medium without subculturing, but the 764 cells tended to detach from the culture dish 10-14 days after plating. The modal chromosome number for cell lines 761, 762, and 763 was 80; that of DDMT-764, 75-79. The amount of virus in the culture fluid was determined by measuring RNA-dependent DNA polymerase activity. Peak virus production by cell lines 762, 763 and 764 was 175%, 62% and 112% of that in parental cell line 761, respectively. Buoyant density of murine mammary tumor virus in sucrose was 1.17 and was clearly distinguishable from the 1.15 of murine leukemia virus. The released virus particles were type B, as confirmed by electron microscopy. (8 refs)
- 79-6967 Viral Expression and Immunogenicity of CBA Mammary Carcinomas and Their Hybrid Lines with an L-Cell Derivative (A9HT). (Eng) Kuzumaki, N. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden); Ber, R.; More, I. A.; Cochran, A. J.; Wiener, F.; Klein, G. *Eur J Cancer* 15(10): 1253-1261; 1979.
- Somatic cell hybrids were obtained by Sendai virus-mediated fusion of a highly tumorigenic variant of L-cell subline A9 of C3H mouse origin (A9HT) and CBA mammary carcinomas SBfnHA and SBfnHC (carried in CBAT6 mice). The presence of biarmed A9HT marker chromosomes confirmed hybridity. Fusion was not between A9HT and stroma cells from CBAT6 mice, as shown by the absence of the T6 marker in both hybrid cell lines (both were spindle cell carcinomas). A9HT and SBfnHA cells expressed mammary tumor virus (MTV)-associated antigens, including major structural component gp52, and murine leukemia virus (MuLV) structural components gp71 and p30 on the cell surface. SBfnHC expressed only gp71. The SBfnHA/A9HT hybrid lost the surface expression of MTV gp52 and MuLV p30, and showed less expression of gp71 than SBfnHA cells. The SBfnHC/A9HT hybrid showed more expression of gp71 than SBfnHC cells. Sensitivity to the cytotoxicity of anti-H-2^k sera was unchanged in all parental and hybrid cell lines. Experiments in CBA mice immunized with heavily irradiated cells and challenged with viable tumor cells showed that the SBfnHA/A9HT hybrid was less immunogenic than SBfnHA, whereas the SBfnHC/A9HT hybrid was slightly more immunogenic than the very poorly immunogenic SBfnHC parent cell line. These results are consistent with the possibility that MTV- and MuLV-associated cell surface antigens influence the immunogenicity of CBA mammary carcinomas. (14 refs)
- 79-6968 A Human Breast Tumor Cell Line (BT-474) that Supports Mouse Mammary Tumor Virus Replication. (Eng) Lasfargues, E. Y. (Inst. Medical Res., Copewood Street, Camden, NJ 08103); Coutinho, W. G.; Dion, A. S. *In Vitro* 15(9): 723-729; 1979.

A human breast tumor cell line (BT-474) derived from an invasive ductal carcinoma was experimentally infected with a mouse mammary tumor virus from the RIII strain (RIII-MuMTV). The virus that replicated in the human cells was characterized as a murine virus by immunofluorescence, electron microscopy and the presence of a specific RNA-directed DNA polymerase; the cells themselves were human according to karyotype and isoenzyme migration patterns. It was concluded that human cells are susceptible to RIII-MuMTV and can eventually support its replication. (22 refs)

- 79-6969 Mouse Mammary Tumor Virus Genome Expression in Chemical Carcinogen-induced Mammary Tumors in Low- and High-Tumor-Incidence Mouse Strains. (Eng) Dusing-Swartz, S. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX 77030); Medina, D.; Butel, J. S.; Socher, S. H. *Proc Natl Acad Sci USA* 76(10): 5360-5364; 1979.
- Mouse mammary tumor virus (MMTV) involvement in 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis was investigated in BALB/c and (BALB/cfC3H mouse strains (having low and high mammary tumor incidences, respectively) which contain endogenous MMTV integrated into the cellular genome. BALB/cfC3H mice are also infected with exogenous MMTV-S (a virulent, milk-transmitted form), which is responsible for a higher incidence of mammary tumors in breeding females. Administration of DMBA (1 mg/wk for 6 wk) to virgin mice of both strains resulted in a moderate frequency of mammary tumors within 40 wk after treatment. No significant differences were found in DMBA-induced tumor incidences at 18 wk (6% and 7%) or at 38 wk (29% and 36%) in BALB/c or BALB/cfC3H mice, respectively. Tumors were assayed for the presence of MMTV RNA by hybridization using MMTV-specific complementary DNA and by immunohistochemical staining utilizing antibodies against MMTV 52,000-dalton glycoprotein, gp52, and 28,000-dalton internal protein, p28. Of 16 BALB/c tumors assayed, 11 did not contain detectable levels of MMTV RNA, while the remaining 5 tumors contained only low levels (0.0005-0.0010%). MMTV RNA was not detected in 5 of 27 BALB/cfC3H tumors; the other BALB/cfC3H tumors contained quantities of MMTV RNA ranging from 0.0006 to 0.4170%. Most BALB/cfC3H tumors with detectable levels of MMTV RNA also synthesized viral proteins gp52 and p28. Thus, expression of the complete MMTV genome is not a prerequisite for maintenance of the tumor phenotype in DMBA-induced mammary tumors in either BALB/c or BALB/cfC3H virgin mice under 1 yr of age. (26 refs)
- 79-6970 Sequence Homology of Nucleic Acids from Human Breast Cancer Cells and Complementary DNA's from Murine Mammary Tumor Virus and Mason-Pfizer Monkey Virus. (Eng) Das, M. R. (Tata Inst. Fundamental Res., Homi Bhabha Road, Colaba, Bombay-400 005, India); Mink, M. M. *Cancer Res* 39(12): 5106-5113; 1979.

Both murine mammary tumor virus (MMTV)- and Mason-Pfizer monkey virus-specific sequences were present simultaneously in nucleic acids isolated from some human breast tumors and from MCF-7 cells, a well-characterized human breast cancer line. Carefully characterized long complementary DNA transcripts were used in the molecular hybridization experiments. The available data suggest that when homology is detected with one of the mammary tumor probes, the other also generally shows

homology. Among all the complementary DNA-RNA hybrids, only three, all MMTV hybrids, showed T_m values (temperatures at which 50% of the total counts were eluted) close to 80 C. The rest of the hybrids were low melting with shallow slopes for their critical temperature curves, indicating partial and imperfect hybrids in the majority of cases. Low levels of weak hybrid formation were also detectable with the tumor DNA's. It cannot be ascertained from the present experiments whether the hybridizing sequences from Mason-Pfizer monkey virus and MMTV code for specific viral functions in their natural hosts. Annealing experiments using gene specific complementary DNA's would be required for full characterization of these sequences. (32 refs)

- 79-6971 Mice with Spontaneous Mammary Tumors Develop Type-specific Neutralizing and Cytotoxic Antibodies Against the Mouse Mammary Tumor Virus Envelope Protein gp52. (Eng) Schochetman, G. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21707); Arthur, L. O.; Long, C. W.; Massey, R. J. *J Virol* 32(1): 131-139; 1979.

Sera from C3H mammary tumor-bearing mice were shown to contain cytotoxic antibodies for mouse mammary tumor virus (MMTV)-producing cells by ^{51}Cr release in a complement-dependent serum cytotoxicity assay. The cytotoxic antibodies could be absorbed by purified C3H MMTV gp52 and C3H MMTV-infected cat cells [C3H (MMTV) CrFK] containing cell surface MMTV gp52. However, purified MMTV p27 and uninfected CrFK cat cells were negative. Absorption of the sera with GR (MMTV) CrFK cells also removed all of the cytotoxicity, whereas absorption with RIII (MMTV) CrFK cells was negative, even though all three infected cat cells contained equivalent amounts of gp52. The same C3H cytotoxic sera also neutralized the focus-forming capacity of a C3H MMTV pseudotype of Kirsten sarcoma virus containing MMTV gp52. In contrast, sera from mammary tumor-bearing GR and RIII mice did not neutralize the pseudotype. Furthermore, neutralization could be achieved only by anti-gp52 but not by anti-gp36, -p27, -p14, or -p10 C3H MMTV sera. The gp52's of C3H, GR, and RIII MMTV could also be distinguished by using a type-specific competition radioimmunoassay employing ^{125}I -gp52 of C3H MMTV and a hyperimmune rabbit anti-C3H MMTV serum. To demonstrate these differences directly, the primary structure of gp52 on the surface of the C3H, GR, and RIII (MMTV) CrFK cells was studied. Two-dimensional tryptic peptide maps of the cell surface lactoperoxidase-catalyzed iodinated gp52's revealed a greater number of peptides common to the gp52's of C3H and GR MMTV's than to RIII MMTV gp52. These results demonstrate that gp52 is a major target antigen for both cytotoxic and neutralizing antibodies, that the cell surface and virion-associated gp52's of C3H, GR, and RIII MMTV contain both group- and type-specific determinants, and that C3H and GR MMTV gp52's are antigenically more related to each other than to RIII MMTV gp52. Furthermore, C3H mammary tumor-bearing mice develop type-specific antibodies capable of recognizing unique gp52 determinants and, therefore, are able to distinguish the gp52 of C3H MMTV from the gp52's of GR and RIII MMTV. (25 refs)

- 79-6972 Mouse Mammary Tumor Virus Infections: Viral Expression and Tumor Risk. (Eng) Altrock, B. W. (Biological Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Cardiff, R. D. *J Natl Cancer Inst* 63(4): 1075-1080; 1979.

Tumor risk status in individual naturally infected BALB/cC3H and BALB/c mice given injections of murine mammary tumor virus (MuMTV) was related to the level of viral antigen in their milk. Two distinct groups of MuMTV-infected mice were identified. The milk of one group contained high viral antigen levels ($\geq 100 \mu\text{g/ml}$), whereas the milk of the other group exhibited low levels ($\leq 3 \mu\text{g/ml}$). Mice that exhibited high levels developed tumors by 17 mo of age, whereas those with low levels did not. Viral expression levels in mice having high risks of tumor development were also related to the length of the latency period preceding overt tumor development. The tumor risk potential of naturally infected mice was frequently that of their mothers. Various doses of MuMTV were injected into BALB/c mice, and the resulting infections differed in latency period, level of viral expression, and potential for neoplastic transformation. (27 refs)

- 79-6973 Expression of MuMTV Antigens in Rabbits and Rats Infected with MuMTV. (Eng) Westenbrink, F. (Radiobiological Inst. TNO, P.O. Box 5815, 2280 HV Rijswijk, Netherlands); Koornstra, W. *Virology* 98(2): 493-496; 1979.

Female rabbits and rats were infected with murine mammary tumor virus (MuMTV) as neonates and later subjected to breeding. Milk samples were collected and tested in competition radioimmunoassays for the MuMTV-antigens gp52 and p28. gp52 was expressed in the milk of 3/8 rats and 1/10 rabbits. p28 was detected in only 2/5 milk samples positive for gp52. (24 refs)

- 79-6974 Abelson Antigen is Expressed on Hematopoietic Spleen Colony-forming Cells from Mice Carrying the Av-2^s Virus Sensitivity Gene. (Eng) Risser, R. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706). *Proc Natl Acad Sci USA* 76(10): 5350-5354; 1979.

The relationship between Av-2 locus and the expression of Abelson antigen was studied in BALB/c x C57BL/6 recombinant inbred mouse strains. Antisera that contained antibody to Abelson antigen were cytotoxic for the spleen colony-forming cells (CFU-S) of adult bone marrow from BALB/c mice. Absorption tests with appropriate tissues and direct cytotoxic tests with bone marrow CFU-S from several mouse strains confirmed that the sensitivity of BALB/c CFU-S to lysis by anti-Abelson-antigen antisera was due to expression of Abelson antigen. Spleen or bone marrow from BALB/c mice undergoing hematopoietic regeneration amplified Abelson antigen expression; no expression of Abelson antigen was observed on regenerating C57BL/B6 bone marrow or spleen. The presence of Abelson antigen on bone marrow cells of seven recombinant inbred strains coincided with the inheritance of sensitivity alleles at the Av-2 locus, a gene that determines susceptibility to Abelson murine leukemia virus (A-MuLV) lymphoma induction. If Av-2 controls expression of Abelson antigen in uninfected mice, then the function of this gene in sensitivity to A-MuLV disease should reflect the physiologic role of Abelson antigen in hematopoietic differentiation. A function consistent with the expression of this determinant is that of a cell surface structure associated with the proliferation and differentiation of particular hematopoietic pathways. (33 refs)

- 79-6975 In Vitro Properties of FBR Murine Osteosarcoma Virus (40650). (Eng) Lee, C. K. (Div. Biological and

Medical Res., Argonne Natl. Lab., Argonne, IL 60439); Chan, E. W.; Reilly, C. A.; Pahnke, V. A.; Rockus, G.; Finkel, M. P. *Proc Soc Exp Biol Med* 162(1): 214-220; 1979.

The in vitro biological properties of the osteosarcoma virus FBR, which was originally isolated from a ^{90}Sr -induced osteosarcoma in an X/Gf mouse, were studied. The virus complex consisted of a transforming component, murine sarcoma virus (MuSV), and a nontransforming component, murine-associated virus (MuAV). Foci of cells transformed by FBR-MuSV(MuAV) were late appearing and consistently showed single-hit focus titration patterns. The isolate was infectious only for murine cells, and it showed distinct b tropism. A clone of transformed cells yielding high-titered sarcoma-rich virus was propagated for the large-scale production of the new virus. Tissue-culture-derived RBR-MuSV(MuAV) possessed osteosarcomagenic properties comparable to those of the parent virus. (26 refs)

- 79-6976 Comparison of the Biological Effects of Anemia Inducing and Polycythemia Inducing Friend Virus Complex. (Eng) Steinheider, G. (Institut für Molekularbiologie und Biochemie, Freien Universität Berlin, Arnimallee 22, D-1000 Berlin, W. Germany); Seidel, H. J.; Kreja, L. *Experientia* 35(9): 1173-1175; 1979.

The biological effects of anemia inducing (FV-a) and polycythemia inducing (FV-p) Friend virus complexes were studied in DBA/2 and BALB/c mice. During leukemogenesis, spleen wt, spleen cell numbers, and reticulocyte numbers increased following infection with either virus. However, the increase was delayed and reticulocytosis less pronounced following FV-a infection than following FV-p infection. Femur cell numbers were moderately increased in FV-a-infected, but not FV-p-infected, mice. At day 8 after infection, the hematocrit was elevated in mice infected with FV-p and slightly reduced in those infected with FV-a; the hematocrit levels continued to diverge with time after infection. Thus, leukemogenesis appeared to be delayed in FV-a-infected mice compared with FV-p-infected mice after injection of comparable quantities of virus. No erythropoietin-independent erythroid precursors (CFU-EI), which are characteristic for FV-p-induced leukemia, were found in the leukemic spleen or bone marrow of FV-a-infected mice. The observed differences, especially the lack of CFU-EI in FV-a-infected mice, might be due to differences in the helper virus component of the FV complex. (16 refs)

- 79-6977 Role of Virus-associated Antigen on Xenogenized Tumor Cell Surface in Production of Antibody Against Tumor-associated Antigen. (Eng) Moriuchi, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Kita-15-jo, Nishi-7-chome, Kita-ku, Sapporo 060, Japan); Kobayashi, H. *Gann Monogr Cancer Res* 23: 65-72; 1979.

The augmentation of the humoral antibody response to virus-infected tumors and the role of virus-associated antigen (VAA) in the production of antitumor antibody were studied. Friend-virus-infected chemically induced rat fibrosarcomas (FV-KMY-17) were incubated with antisera against tumor-associated antigen (TAA), VAA, or histocompatibility antigen (Rw). Modulation of TAA occurred rapidly, whereas Rw was modulated very slowly, suggesting that TAA and Rw have a different mobility on the cell surface. Antigenic modulation of VAA was induced by a different mechanism involving shedding of the antigen-antibody complex.

FV-KMT-17 was incubated with antiserum against TAA and antisera against VAA or Rw plus complement. Inhibition of lysis was observed with anti-VAA but not with anti-Rw, suggesting that there is an association between TAA and VAA but not between TAA and Rw. Immunization with FV-KMT-17 or non-virus-infected KMT-17 produced the same primary antibody response against TAA. In the secondary response, however, immunization with FV-KMT-17 produced a significantly higher antibody level than immunization with KMT-17. TAA and VAA may associate to form immunogenic units, with VAA functioning as a helper determinant. (7 refs)

- 79-6978 Susceptibility of Japanese Mouse Strains to Murine Leukemia Viruses. (Eng) Hoshino, H. (Dept. Oncology, Inst. Medical Science, Univ. Tokyo, Shirogane-dai, Minato-ku, Tokyo 108, Japan); Yamamoto, T. *Jpn J Exp Med* 49(4): 293-294; 1979.

Susceptibility to the murine leukemia viruses (MuLV) was investigated in the following Japanese mouse strains: FM, KK, KOMA, NC, RR, SII, SS, and TES. All strains were susceptible to infection with both N- and NB-tropic MuLV, but they showed different degrees of resistance to B-tropic MuLV. The genotypes of these strains appeared to be *Fv-1nn* and *Fv-4ss*. Two- to three-month old mice of each of the test strains and of strains DDD, C57BL/6, and C3H were inoculated ip with 0.2 ml of a 10% extract of spleen infected with N-tropic Friend leukemia virus. All strains except C57BL/6 developed splenomegaly. The genotype of C57BL/6 has been demonstrated to be *Fv-2rr*, indicating that the other strains carry the genotype *Fv-2ss* and *Fv-4ss*. Embryo cells of the eight test strains were completely resistant to infection with xenotropic murine sarcoma-leukemia virus complex, as assessed by focus formation. (10 refs)

- 79-6979 Protein Composition of a Defective Murine Sarcoma Virus Particle Possessing the Enveloped Type-A Morphology. (Eng) Pinter, A. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); deHarven, E. *Virology* 99(1): 103-110; 1979.

The protein composition of a noninfectious murine sarcoma virus (Gazdar MSV) isolated from the HTG2 cell line was characterized. Electron microscopy of thin sections of the infected cells showed that the virus particles were assembled via the budding mechanism at the plasma membrane; the released virions possessed almost exclusively the enveloped type-A morphology characteristic of the immature form of retrovirus particles. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the virions under reducing conditions revealed a nonglycosylated protein of approx 65,000 daltons, p65. When analyzed under nonreducing conditions this band was resolved as well. Immunoprecipitation of p65 was accomplished with monospecific antisera against the individual "gag" gene-coded MuLV proteins p30, p15, and p12 but not with antisera against the MuLV envelope proteins, reverse transcriptase, or p10, indicating that the MSV p65 is related to but not identical with the Pr65(gag) of MuLV. The processed MuLV core proteins were not observed in purified HTG2 virions or in HTG2 cell extracts; thus proteolytic cleavage of the precursor is not required for the assembly or release of the MSV particles. Immunoprecipitation of lysed virions and HTG2 cell lysates with antisera to the MuLV envelope proteins gp70 and p15(E) demonstrated that detectable amounts of these and immunologically related components are not present in the virions

and are not expressed in the infected cells. It is suggested that the envelope proteins are not essential for the assembly and release of budding retrovirus particles. (16 refs)

- 79-6980 **Viral Specificity of H2-Restricted T Killer Cells Directed Against Syngeneic Tumors Induced by Gross, Friend, or Rauscher Leukemia Virus.** (Eng) Plata, F. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY 10461); Lilly, F. *J Exp Med* 150(5): 1174-1186; 1979.

Cytolytic T lymphocytes (CTL) were generated against murine tumors induced by Gross, Friend, or Rauscher leukemia virus (LV) in syngeneic mixed leukocyte-tumor cell cultures. Tumor cells induced by Friend, Moloney, or Rauscher (FMR) virus and positive for the FMR antigen were killed by syngeneic CTL immune to any one of these three LV; the same CTL, however, could not kill syngeneic tumor cells induced by Gross LV. Gross-specific CTL were specific for syngeneic tumor cells expressing the Gross-virus-associated cell-surface antigen (GCSA) and not the FMR antigen. These patterns of CTL tumor specificity were true for mice of the H-2^b haplotype and of the H-2^d haplotype. Mice of the H-2^d haplotype consistently gave weak but specific CTL responses to syngeneic Gross LV-induced tumor cells. Attempts were made to map the H-2 restriction that accompanied the tumor specificity of the Gross LV-specific CTL. The results indicated that H-2^b CTL from BALB.B mice recognized Gross LV-induced tumor antigens in association with H-2 determinants coded by either H-2K^b or H-2D^b genes. However, H-2^d CTL from BALB/c mice were restricted to recognition of Gross LV-induced tumor antigens in association with H-2K^d; association with H-2D^d did not lead to significant killing by CTL. This pattern of specificity for H-2K and H-2D antigens is somewhat different from that seen in FMR-specific CTL. (29 refs)

- 79-6981 **Murine Leukemia Virus-associated Cell Surface Antigens in Rats Neonatally Infected With Gross Murine Leukemia Virus.** (Eng) Basch, R. S. (Dept. Pathology, New York Univ. Medical Center, 550 First Avenue, New York, NY 10016); Grausz, D.; Harris, N.; Mitchison, N. A. *J Natl Cancer Inst* 63(6): 1485-1492; 1979.

The appearance of cells positive for viral protein antigens (VPA) in the organs of newborn W/F, Lew, AS, and DA rats treated with Gross murine leukemia virus (MuLV) was studied. Most cells within the spleen and thymus and many cells within the bone marrow were positive for VPA 2 wk after MuLV treatment. Significant numbers of VPA-positive thymocytes were found in most animals by 3-4 wk. As the animals grew older, there was a modest increase in the number of VPA-positive cells in the spleen and thymus and a considerable increase in the intensity of fluorescent staining for VPA. Cells that were strongly positive for p30 antigen were found only among the leukemic thymocytes. Spleen cells with the strongest fluorescence had the properties of T cells, but VPA were also demonstrated on non-T-cells in both the spleen and bone marrow. VPA appeared to be actually synthesized by these cells and was not associated with the passive absorption of intact virus. The VPA-positive population expanded long before malignant cells could be detected in the rats and, in most animals, the entire T-cell compartment became VPA positive. These animals were unable to respond to MuLV antigens, and many eventually developed leukemia. However, some rats apparently broke the tolerance that followed neonatal infection and eliminated VPA positive cells from their tissues. (24 refs)

- 79-6982 **Physical Map of Biologically Active Harvey Sarcoma Virus Unintegrated Linear DNA.** (Eng) Goldfarb, M. P. (Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Weinberg, R. A. *J Virol* 32(1): 30-39; 1979.

BALB/c JLS V9 cells infected with Harvey sarcoma virus-murine leukemia virus (HSV-MuLV) complex contained unintegrated HSV linear DNA of 6.0-kilobase (kb) pair mass. The cells also contained two HSV closed circular DNA species along with MuLV-encoded linear and closed circular DNA species. HSV 6.0-kb pair linear DNA induced focal transformation upon transfection of NIH 3T3 mouse fibroblasts, and the biological activity of HSV DNA did not require helper MuLV functions. A physical map of restriction endonuclease cleavage sites along HSV 6.0-kb pair linear DNA was derived. Comparison of this map with one for Moloney MuLV DNA showed that the HSV and Moloney MuLV genomes are identical near their viral RNA 3' ends. (30 refs)

- 79-6983 **The Effect of Malignant Transformation on the Sensitivity of Murine Fibroblasts to the Antiviral Effect of Interferon.** (Eng) Morris, A. G. (Dept. Biological Sciences, Univ. Warwick, Coventry, CV4 7AL, England); Barrett, A. D.; Bird, R. M.; Burke, D. C. *FEMS Microbiol Lett* 6(3): 139-141; 1979.

Interferon (IF) was titrated in L cells and in a variety of transformed and untransformed murine fibroblast lines using a method involving inhibition of nucleic acid synthesis. The IF sensitivity of the cell line was expressed as the ratio of the IF titer in the cell line to the titer in L cells (3369). Normal NIH 3T3 cells were slightly less sensitive to IF than L cells, but all transformed clones derived from NIH 3T3 cells were at least 10-fold less sensitive than NIH 3T3. Similar results were obtained with normal mouse embryo fibroblasts and their transformed derivatives and with BALB/c 3T3 cells and transformed derivatives. Infection of NIH 3T3 cells by the Kirsten strain of murine leukemia virus (MLV) in the absence of transformation did not significantly change the sensitivity to IF. Incubation of IF overnight with cultures of NIH 3T3 cells and three of its MSV-transformed derivatives showed that IF is as stable in the presence of transformed cells as in the presence of untransformed cells. The data indicate that malignant transformation of murine fibroblasts reduces their intrinsic sensitivity to the antiviral effect of IF. It is suggested that the change of sensitivity is caused by an effect at some step early in the pathway of the action of IF, possibly at the level of the cell surface receptor for IF. (10 refs)

- 79-6984 **A Detailed Model of Reverse Transcription and Tests of Crucial Aspects.** (Eng) Gilboa, E. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA 02139); Mitra, S. W.; Goff, S.; Baltimore, D. *Cell* 18(1): 93-100; 1979.

A model of reverse transcription is described by which the detailed architecture of 10 molecular structures is predicted. The model includes a number of novel features for which experimental evidence is presented. Growing minus DNA strand is copied from the viral RNA only up to a position about 150 nucleotides from the 5' end of the RNA. Plus-strand DNA, after being copied from approx 600 nucleotides at the 5' end of the minus-strand DNA, then transcribes the first approx 20 nucleotides of the transfer RNA^{pr} primer (which is covalently attached to the 5' end of the minus DNA

strand). The 3' ends of the minus and plus DNA probably form a hybrid through the homology conferred by the primer binding site sequences. The minus and plus DNA strands are elongated in a continuous fashion resulting in a linear double-stranded DNA molecule containing a 600-nucleotide direct repeat at both ends. Thus, most of the features of the model have experimental support, and it appears to provide a credible description of reverse transcription. (29 refs)

- 79-6985 Viral Genome RNA Serves as Messenger Early in the Infectious Cycle of Murine Leukemia Virus. (Eng) Shurtz, R. (Dept. Life Sciences, Bar-Ilan Univ., Ramat-Gan, Israel); Dolev, S.; Aboud, M.; Salzberg, S. *J Virol* 31(3): 668-676; 1979.

When NIH/3T3 mouse fibroblasts were infected with the Moloney strain of murine leukemia virus, part of the genome RNA molecules were detected in the polyribosomes of the infected cells early in the infectious cycle. The binding appeared to be specific, since the release of viral RNA from polyribosomes was demonstrated with EDTA. When infection occurred in the presence of cycloheximide, most viral RNA molecules were detected in cytoplasm free of nuclei and polyribosomes. Size analysis on polyribosomal viral RNA molecules indicated that two size class molecules, 38S and 23S, were present in polyribosomes 3 hr after infection. Analysis of the polyribadenylate [poly(rA)] content of viral RNA extracted from infected polyribosomes demonstrated that such molecules bind with greatest abundance 3 hr after infection, as has been detected with total viral RNA. No molecules lacking poly(rA) stretches were detected in polyribosomes. Furthermore, when a similar analysis was performed on unbound molecules present in the free cytoplasm, identical results were obtained. It is concluded that no selection towards poly(rA)-containing viral molecules occurs on binding to polyribosomes. These findings suggest that the incoming viral genome of the Moloney strain of murine leukemia virus may serve as a messenger for the synthesis of one or more virus-specific proteins early after infection of mouse fibroblasts. (40 refs)

- 79-6986 Transcription of Endogenous C-Type Viruses in Resting and Proliferating Tissues of BALB/Mo Mice. (Eng) Jaenisch, R. (Heinrich Pette-Institut für Experimentelle Virologie und Immunologie, Universität Hamburg, Martinistrasse 52, 2000 Hamburg 20, W. Germany); Hoffmann, E. *Virology* 98(2): 289-297; 1979.

The effect of tissue proliferation on the genome expression of endogenous C-type viruses was studied. Liver cell proliferation was induced by partial hepatectomy in BALB/Mo mice. RNA sequences homologous to two classes of C-type viruses, to the Moloney leukemia virus (M-MuLV) endogenous in BALB/Mo mice, and to the xenotropic endogenous BALB 2 virus, were quantitated by molecular hybridization. RNA from resting liver tissue contained low concentrations of sequences homologous to either class of virus. No substantial increase in virus-specific RNA concentration was observed in regenerating livers between 18 hr and 5 days. The effects of liver cell proliferation on de novo infection with Moloney leukemia virus was studied. The number of M-MuLV-specific DNA copies in the livers of viremic BALB/c mice infected with virus as newborns did not change following partial hepatectomy. These results indicate that neither tissue-specific expression of M-MuLV in BALB/Mo mice nor organ-specific de novo infection with M-MuLV is dependent on the proliferative

state of the cells. This is consistent with the hypothesis that tissue-specific activation of the virus is dependent on regulatory mechanisms involved in cellular differentiation. (23 refs)

- 79-6987 Immunochemical Characterization of Tumor-associated Surface Antigens on a Moloney Leukemia Virus-Lymphoma, MBL-2. (Eng) Ng, A. K. (Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD 20014); McIntire, K. R.; Suzuki, S.; Aoki, T.; Herberman, R. B. *Int J Cancer* 24(4): 504-512; 1979.

Tumor-associated surface antigens (TASA) on the Moloney leukemia virus (M-MuLV)-induced lymphoma MBL-2 in C57BL/6 mice (B6) were characterized. The surface proteins of MBL-2 cells were selectively radioiodinated and then extracted by Nonidet P40. The solubilized materials were reacted with a variety of antisera: monospecific antisera to murine leukemia viral proteins (anti-gp69/71, anti-p30, anti-p15, anti-p12, and anti-p10), sera from B6 which regressed murine sarcoma tumors induced by murine sarcoma virus (anti-MSV) and a rabbit anti-MBL-2 antiserum. The resulting radioimmune precipitates were analyzed and compared in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDA-PAGE). Among all anti-viral protein antisera tested, only anti-gp69/71 was active, detecting a protein doublet of gp69/71 and its degradation fragments of 42,000 and 35,000 daltons. Radioimmune precipitates prepared with anti-MSV showed a SDS-PAGE pattern similar to that seen with anti-gp69/71. This result indicated that the surface antigen detected by the anti-MSV serum on MBL-2 tumor cell was probably a viral envelope antigen. The rabbit-anti-MBL-2 serum detected on the cell membrane an antigen of approx 95,000 daltons which was tumor-associated and did not appear to be related to virion components. The anti-MBL-2 serum still reacted with the 95,000 dalton antigen after absorption with disrupted M-MuLV virus and with gp69/71 and p30 purified from the virus. (46 refs)

- 79-6988 Effect of Anti-Mouse Type-I Interferon Globulin on the Evolution of Moloney Sarcoma Virus Induced Disease in Mice. (Eng) Ingnot, A. D. (Lab. Tumour Virology, Dept. Immunology, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Wrocław, Poland); Ingnot, O.; Zoltowska, A.; Oleszak, E. *Int J Cancer* 24(4): 445-449; 1979.

The prolonged administration of potent sheep anti-mouse type-I interferon globulin (anti-IF IgG) had a marked potentiating effect on Moloney sarcoma virus (MSV) infection in mice. The extent of resistance to the MSV-induced disease was age-related. In 4-wk-old BALB/c mice, anti-IF IgG consistently induced 70%-80% mortality due to the progression of early or late tumors and erythroleukemia, whereas mortality of control mice was significantly lower. The same effect was obtained in 1-yr-old BALB/c mice. However, in 4-wk-old C57BL/6 or 6-wk-old BALB/c mice, anti-IF IgG enhanced only the growth of early tumors but had no effect on their regression. Antigenic stimulation with normal sheep globulin suppressed the growth of early tumors in suckling BALB/c or C57BL/6 mice and enhanced the evolution of late MSV-induced disease in older mice. (12 refs)

- 79-6989 The Integration Sites of Endogenous and Exogenous Moloney Murine Leukemia Virus. (Eng) van der Put-

ten, H. (Lab. Biochemistry, Univ. Nijmegen, Geert Grooteplein 21 Noord, Nijmegen, Netherlands); Terwindt, E.; Berns, A.; Jaenisch, R. *Cell* 18(1): 109-116; 1979.

Specific complementary DNA (cDNA) probes of Moloney and AKR murine leukemia viruses were prepared to characterize the proviral integration sites of these viruses in the genomes of Balb/Mo and Balb/c mice. The genetically transmitted Moloney provirus of Balb/Mo mice was detected in a characteristic Eco RI DNA fragment of 16×10^6 daltons. No fragment of this size was detected in tissue DNA from BALB/c mice infected as newborns with Moloney virus. The authors conclude that a viral integration site, occupied in preimplantation mouse embryos, is not necessarily occupied when virus infects cells in postnatal animals. Balb/Mo and Balb/c mice did carry the AKR structural gene in an Eco RI DNA fragment of 12×10^6 daltons. Further restriction analysis of this fragment indicated that both mouse lines carried one AKR-type provirus. Leukemogenesis in Balb/Mo and newborn infected Balb/c mice was accompanied by reintegration of Moloney viral sequences in new chromosomal sites of tumor tissues. Part of the reintegrated Moloney viral sequences were of subgenomic size. The AKR viral sequences, however, were not found in new sites. Further restriction analysis revealed that the development of Moloney virus-induced leukemia in BALB/Mo mice did not lead to detectable structural alteration of the genetically transmitted Moloney and AKR structural genes. (30 refs)

79-6990 Characterization of 40,000- and 25,000-Dalton Intermediate Precursors to Rauscher Murine Leukemia Virus *gag* Gene Products. (Eng) Naso, R. B. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Karshin, W. L.; Wu, Y. H.; Arlinghaus, R. B. *J Virol* 32(1): 187-198; 1979.

Under steady-state labeling conditions, Rauscher murine leukemia virus-infected NIH Swiss mouse cells contain at least three major polyproteins [pPr65(gag), Pr40(gag), and pPr25(gag)] derived from the viral *gag* gene and having mol wts of 65,000, 40,000, and 25,000. pPr65(gag) has been shown previously to contain all four core proteins (p15, pp12, p30, and p10). Pr40(gag) was found to contain p30 and p10 antigenic determinants and peptide sequences. The rapidly labeled precursor proteins Pr40(gag) and pPr25(gag) were detectable early in pulse-chase experiments. Both precursors disappeared during the later stages of the chase period concurrent with the appearance of the mature viral core proteins. pPr65(gag) and pPr25(gag) were phosphorylated, pPr25 having a higher specific ^{32}P activity than pPr65. Nevertheless, peptide mapping studies, as well as the identification of the phosphorylated amino acid residues of pPr65, pPr25, and pp12, indicated that the same sites are phosphorylated regardless of whether the precursors or the mature pp12 are examined. (25 refs)

79-6991 Rauscher Leukemia Virus-induced Tumor Antigens: Complete Separation from gp70, p30 and H-2. (Eng) Alaba, O. (Lab. Cell Biology, NCI, Bethesda, MD 20205); Rogers, M. J.; Law, L. W. *Int J Cancer* 24(5): 608-615; 1979.

The possibility that the viral proteins gp70 and p30 and the histocompatibility antigen H-2 may function as the tumor-specific transplantation antigen (TSTA) of the Rauscher murine leukemia virus-induced leukemia RBL-5 and also in the secondary in vitro induction of cytotoxic T lymphocytes (CTL) was investigated. The antigen was obtained by plasma membrane isolation of RBL-5

cells and solubilization with sodium deoxycholate followed by gel filtration chromatography. A fraction containing excellent tumor-rejection activity but low amounts of gp70, p30, and H-2 was chromatographed on goat anti-gp70, goat anti-p30, and sheep anti-H-2(b) immunoaffinity columns. The data obtained indicate that neither gp70, p30, nor H-2 functions as the TSTA of RBL-5 leukemia, neither individually nor as a complex. Similarly, the antigen responsible for the specific secondary induction of CTL in vitro was shown to be distinct from these three proteins. (38 refs)

79-6992 Interactions Between Cellular Membrane Receptors and Oncovirus Envelope Glycoprotein: Influence of Enzymes and Protein-modifying Reagents on Receptors. (Eng) Bishayee, S. (Indian Inst. Experimental Medicine, Calcutta-700032, India); Strand, M. *Prog Clin Biol Res* 31: 721-731; 1979.

Binding of purified envelope glycoprotein (gp69/71) of Rauscher murine type C oncovirus to cellular membrane receptors was analyzed with reaction systems using intact cells or membranes of disrupted cells. The reaction was highly specific; only cells permissive of infection by Rauscher virus bound the ^{125}I -labeled viral glycoprotein. The specificity of binding was also demonstrated with respect to virus interference; cells productively infected with murine ecotropic type C virus failed to bind the virus envelope glycoprotein, whereas permissive cells infected with murine xenotropic virus continued to bind the Rauscher ecotropic virus glycoprotein. The reaction required the presence of Ca^{2+} or Mn^{2+} and was rapid and reversible. Studies of the enzymatic digestion of membranes suggested that the receptor is a protein which requires lipid either for its activity or for the integrity in the membrane. Receptor binding was greatly reduced by modification of histidine, tyrosine, and tryptophan residues. (26 refs)

79-6993 Identification of the Major Structural Proteins of Two BALB/c Myeloma C-Type Viruses. (Eng) Spriggs, D. R. (Div. Tumor Biology, Christ Hosp. Inst. Medical Res., 2141 Auburn Ave., Cincinnati, OH 45219); Krueger, R. G. *Virology* 98(1): 35-44; 1979.

The structural proteins of the C-type viruses produced by cloned lines of the MOPC-21 and FLOPC-1 BALB/c murine myelomas were studied. The viruses, designated MO₂₁-MuMAV and FL₁-MuMAV, respectively, were composed of proteins with mol wts of approx 99,000, 75,000, 17,000, 12,000, and 10,000 daltons. In addition, the viruses contained a "doublet" of a mol wt of approx 30,000 daltons. The 90,000- and 75,000-mol wt proteins were glycosylated. The p30 doublet and the original NB ecotropism were retained on subsequent virus cloning in SC-1 cells, passage through NIH-3T3 or BALB/3T3 cells, and microtiter plate cloning of SC-1 cells replicating cloned virus. Cloning the viruses in SC-1 cells resulted in potentiation of the ability of the viruses to replicate in these cells. The two cloned MuMAVs appeared to possess the p30 proteins previously described in endogenous BALB/c N- and B-tropic viruses. Tryptic peptide analysis of the myeloma virus p30 proteins demonstrated that the proteins shared extensive homology with, but not identity to, the two prototype BALB/c ecotropic endogenous viral p30 proteins. (25 refs)

79-6994 Apparent Posttranscriptional Block to Anaerobic Induction of Endogenous Leukemia Virus. (Eng) Whitaker-Dowling, P. A. (Dept. Microbiology, Univ. Pittsburgh

Sch. Medicine, Pittsburgh, PA 15261); Marotti, K. R.; Anderson, G. R. *J Virol* 32(1): 234-239; 1979.

Uninfected Fischer rat cells were induced by anaerobic stress to transcribe high levels of endogenous type C leukemia virus RNA. Complete 35S virus RNA with attached polyadenylic acid sequences was found associated with polysomes, indicating functional messenger RNA. The fact that no mature virus was released under these conditions indicates the presence of a posttranscriptional block to complete virus synthesis. (15 refs)

79-6995 Persistence and Expression of Herpes Virus in Guinea Pig B and T Spleen Cells. (Eng) Griffith, B. P. (Dept. Lab. Medicine, Yale Univ. Sch. Medicine, New Haven, CT 06516); Hsiung, G. D. *Proc Soc Exp Biol Med* 162(1): 202-206; 1979.

The role of spleen lymphocytes in acute and latent infection with guinea pig herpes-like virus (GPHLV) and the in vitro susceptibility of these lymphocytes to GPHLV were explored. Macrophage-, B-cell-, and T-cell-enriched populations obtained from infected guinea pigs were examined for infectious GPHLV. During acute infection, virus was first detected in the macrophage and B-cell fractions and was evident in the T-cell fraction only 5 days or more after infection. During latent infection, infectivity titers in the B fractions were consistently higher than in the T fractions. In both the B and T lymphocytes derived from latently infected guinea pigs, virus was expressed only after in vitro cultivation or cocultivation with susceptible cells. Lymphocytes infected in vitro did not support GPHLV replication, although latent infection of lymphocytes with GPHLV was readily accomplished in vivo. (21 refs)

79-6996 Conserved Polynucleotide Sequences Among the Genomes of Papillomaviruses. (Eng) Law, M. F. (Lab. Pathology, NCI, Bethesda, MD 20205); Lancaster, W. D.; Howley, P. M. *J Virol* 32(1): 199-207; 1979.

DNA from various papillomaviruses were analyzed for nucleotide sequence homology. Under standard hybridization conditions [melting temperature (T_m) -28 C], no homology was detectable among the genomes of human papillomavirus type 1 (HPV-1), bovine papillomavirus type 2 (BPV-2), or cottontail rabbit (Shope) papillomavirus (CRPV). However, under less stringent conditions (ie, T_m -43 C), stable hybrids were formed between radiolabeled DNAs of CRPV, BPV-1, or BPV-2 and the *Hind*III-*Hpa*I A, B, and C fragments of HPV-1. Under these same conditions, radiolabeled CRPV and HPV-1 DNAs formed stable hybrids with the *Hind*III B and C fragments of BPV-2 DNA. These results indicate that there are regions of homology with as much as 70% base match among all of these papillomavirus genomes. Furthermore, unlabeled HPV-1 DNA competitively inhibited the specific hybridization of radiolabeled CRPV DNA to BPV-2 DNA fragments, indicating that the homologous DNA segments are common among these remotely related papillomavirus genomes. These conserved sequences are specific for the *Papillomavirus* genus of papovaviruses, as evidenced by the lack of hybridization between HPV-1 DNA and either simian virus 40 or human papovavirus BK DNA under identical conditions. These results indicate a close evolutionary relationship among the papillomaviruses and further establish the papillomaviruses and polyoma viruses as distinct genera. (35 refs)

79-6997 Serological Relationship of Woodchuck Hepatitis Virus to Human Hepatitis B Virus. (Eng) Werner, B. G. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Smolec, J. M.; Snyder, R.; Summers, J. *J Virol* 32(1): 314-322; 1979.

Two antigenic systems of the woodchuck hepatitis virus were identified. The relationship between viral antigens of the woodchuck hepatitis virus and the human hepatitis B virus was determined by using immunoprecipitation, hemagglutination, and immune electron microscopic techniques. Antigens found on the cores of the two viruses were cross-reactive. Lack of cross-reactivity between the surface antigens of the two viruses in immunodiffusion experiments suggested that the major antigenic determinants of the viral surfaces are different; however, results of passive hemagglutination tests indicated that there are common minor determinants. Nucleic acid homology, as measured by liquid hybridization, was found with 3-5% of the viral genomes. These results provide further evidence that woodchuck hepatitis virus is the second member of a new class of viruses represented by human hepatitis B virus. Since virus-infected woodchucks may acquire chronic hepatitis and hepatocellular carcinoma, these antigens and their respective antibodies will be useful markers for following the course of virus infection in investigations of the oncogenic potential of this class of viruses. The nucleocapsid antigen described may be a class-specific antigen of these viruses and thus may be useful in identifying members of the group. (17 refs)

79-6998 Physical Maps of Bovine Papillomavirus Type 1 and Type 2 Genomes. (Eng) Lancaster, W. D. (Dept. Surgery, Div. Otolaryngology, Case Western Reserve Univ., Cleveland, OH 44106). *J Virol* 32(2): 684-687; 1979.

Physical maps of bovine papillomavirus types 1 and 2 (BPV-1 and BPV-2) DNA were constructed from analysis of the electrophoretic mobilities of restriction endonuclease cleavage fragments from dual digests. BPV-1 DNA was sensitive to *Hind*III, *Hind*II, *Eco*RI, *Hpa*I, and *Bam*HI, with all but *Hind*III yielding single scissions. BPV-2 DNA was resistant to *Eco*RI; *Hind*III had one cleavage site, whereas *Hpa*I, *Bam*HI, and *Hind*II yielded multiple fragments. DNA from one of four BPV-1 isolates examined was resistant to *Hind*III, while another DNA isolate was resistant to *Bam*HI. The three BPV-2 isolates examined were uniformly sensitive to the restriction endonucleases employed. (11 refs)

79-6999 Enhancement of Feline Leukemia Virus-induced Leukemogenesis in Cats Exposed to Methylnitrosourea. (Eng) Schaller, J. P. (Dept. Veterinary Pathology, Ohio State Univ., Columbus, OH); Mathes, L. E.; Hoover, E. A.; Olsen, R. G. *Int J Cancer* 24(5): 700-705; 1979.

The effect of methylnitrosourea (MNU, 15-20 mg/kg, iv) on the susceptibility of young adult specific-pathogen-free cats to infection and induction of oncornavirus disease by the Rickard strain of leukemia virus (FeLV, inoculated ip or oronasally) was studied. Of eight cats injected with MNU plus FeLV, six developed persistent viremia, and five of the six became debilitated from thymic lymphomas. Only one of six non-MNU-treated cats of the same age became transiently viremic. Development of antibody to feline oncornavirus-associated cell membrane antigen was markedly depressed in the cats given MNU plus FeLV as compared with cats inoculated with FeLV alone. The data show that MNU was ap-

parently responsible for the obliteration of the age-related resistance in cats to FeLV infection and induction of FeLV-related disease; in nature, exposure to toxic chemical carcinogens may act as factors in determining susceptibility to feline oncornavirus in the cat. (33 refs)

- 79-7000 Susceptibility of Human Cell Lines to Feline Leukemia Virus and Feline Sarcoma Virus. (Eng) Azocar, J. (Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); Essex, M. *J Natl Cancer Inst* 63(5): 1179-1184; 1979.

The susceptibility of human fibroblasts (WI-38) and various human lymphoid cell lines to feline-leukemia virus (FeLV) and feline-sarcoma virus (FeSV) was investigated. Human cells were highly sensitive to infection by FeLV subgroups B and C and by FeSV but resistant to infection by FeLV subgroup A. The cells became infected, produced infectious virus, and displayed no difference in morphology or viability. T-cell lines appeared to be more sensitive to FeLV and FeSV infection and to produce more virus than did autochthonous B-cells. B-cell lines with membrane IgG appeared more resistant to infection than did those with no membrane. (33 refs)

- 79-7001 Further Characterization of the Oncornavirus Inactivating Factor in Normal Mouse Serum. (Eng) Montelaro, R. C. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC 27710); Fischinger, P. J.; Larrick, S. B.; Dunlop, N. M.; Ihle, J. N.; Frank, H.; Schafer, W.; Bolognesi, D. P. *Virology* 98(1): 20-34; 1979.

The oncornavirus inactivating factor (OIF) contained in the normal sera of certain mouse strains was investigated. The OIF copurified quantitatively with the lipoprotein fraction of STU mouse serum subjected to flotation through sucrose density gradients. The buoyant material consisted of a heterogeneous population of spherical particles (200-1200 Å) that had a density of <1.006 g/ml, an apparent mol wt of $0.5-1 \times 10^7$, and contained triglyceride as the predominant (>70%) lipid moiety. In contrast to whole serum, which specifically inactivated xenotropic and polytropic murine oncornaviruses, the isolated low-density lipoprotein (VLDL) fraction was also able to inactivate murine ecotropic and feline leukemia viruses. Fractionation of STU lipoproteins or whole serum by extraction with ether:ethanol removed the OIF into the organic solvent. This factor extract inactivated the same spectrum of viruses as serum VLDL. However, sodium dodecyl sulfate-polyacrylamide gel electrophoretic analysis of unlabeled and radioiodinated factor extracts revealed no detectable protein components. NIH Swiss mouse sera harbored high titers of factor in an inactive form that displayed activity upon flotation or after extraction with ether:ethanol. This phenomenon was specific for this sera. No apparent significant reduction of OIF titer was observed in serial examinations of AKR mice during preleukemia or leukemia or in individual C57BL mice before and during the development of radiation-induced leukemia. (51 refs)

- 79-7002 Requirement of Human Chromosomes 19, 6 and Possibly 3 for Infection of Hamster x Human Hybrid Cells with Baboon M7 Type C Virus. (Eng) Brown, S. (Dept.

Biochemistry, Univ. Hosp. Medical Sch., Nottingham, England); Oie, H. K.; Gazdar, A. F.; Minna, J. D.; Francke, U. *Cell* 18(1): 135-143; 1979.

The replication pattern of the endogenous baboon type C virus M7 was studied in 29 primary Chinese hamster x human hybrid clones generated with leukemic cells from two patients with acute lymphoblastic and myeloblastic leukemia, respectively. There was no evidence of viral particulate RNA-dependent DNA polymerase (RDDP) or M7 antigen before viral infection. M7 virus replicated in human and some hybrid cells but not in Chinese hamster cells, indicating that M7 requires dominantly expressed human gene(s) for replication. Enzyme and cytogenetic analyses showed that a gene(s) coded for by human chromosome 19 is necessary for M7 infection of these hybrids. Detailed cytogenetic correlations revealed, however, that the chromosome 19+ /M7+ hybrid clones with intact chromosomes also had copies of chromosomes 3 and 6. Previously, *Bevi*, the putative integration site for M7 virus, was assigned to human chromosome 6. However, many clones with various combinations of chromosomes 3 and 6 lacked chromosome 19 and failed to replicate exogenously applied M7 virus, while tests of 27 secondary clones showed that M7 markers co-segregated with chromosome 19 markers. These findings all confirm the need for a chromosome 19-coded function in Chinese hamster x human hybrids. In addition, the yield of viral particulate RDDP produced into the culture fluid was 50- to 100-fold less per viral antigen-positive cell in the hybrids compared with human cells. Thus some form of regulation of viral components exists in the hybrid cells. When the virus replicating in hybrid cells was transferred back to human cells, this regulation was relaxed and the yield of RDDP per FA(+) cell greatly increased. It is concluded that human chromosomes 6 and 19 code for functions involved in M7 virus metabolism, and a function coded for by chromosome 3 cannot be excluded. (25 refs)

- 79-7003 Similarities in the Structural Organization of the Genomes of Stumptailed Macaque Virus (Strain HD) and Simian Virus 40. (Eng) Chowdhury, K. (Institut für Virusforschung, German Center Cancer Res., 6900 Heidelberg, W. Germany); Ammann, E.; Sauer, G. *J Gen Virol* 45(1): 223-226; 1979.

Previous studies showed that HD virus isolated from a tissue culture line of *Cercopithecus aethiops* origin has a genome consisting of a large size class with an extra fragment and a small class identical to the genome of stump-tailed macaque virus. Serological studies showed that HD virus-producing cells shared a common capsid antigen with all other members of the simian virus 40 (SV40)-polyoma subgroup of papovaviruses. To determine possible homologies between HD and SV40 viral genomes, HD virus DNA from a clonal line of Vero-76 cells that produce only the larger DNA class was digested with restriction endonucleases. The resulting five fragments A to E were hybridized with nick-translated ³²P-SV40 DNA and subjected to autoradiographic analysis. HD DNA fragments B, C, and D possessed homology to SV40 DNA, but the large fragment A and the small fragment E (missing in the small HD genome) lacked discernible homology. When the SV40 C fragment, which represents the origin of DNA replication was hybridized with HD DNA, homology was limited to the HD fragment C. Further experiments revealed homology between SV40 fragments coding for the VP1 capsid protein and HD fragment D. It is concluded that SV40 polynucleotide sequences that share homologies with the HD genome are confined to the late region and the origin of DNA replication. (16 refs)

79-7004 Syncytia Formation of Human Transformed Cell Lines by Simian Sarcoma Virus Type I (SSV-I/SSAV-I). (Eng) Ocho, M. (Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan); Ogura, H.; Tanaka, T.; Oda, T. *Acta Med Okayama* 33(2): 137-140; 1979.

The induction of syncytia formation by simian sarcoma virus type I and simian sarcoma associated virus type I complex (SSV-I/SSAV-I) was investigated in human cultured cells originating from malignant tumors, virus-transformed cells, or normal embryonic cells. HeLa, HEP-2, and KB cells, which were derived from human malignant tumors, formed syncytia when cocultivated with SSV-I/SSAV-I-producing human embryonic lung (HEL) cells. KC cells (a human glioma cell line transformed by Rous sarcoma virus, RSV, and RSb cells (human embryonic cells transformed by simian virus 40 and RSV) also formed syncytia when cocultivated with SSV-I/SSAV-I-producing HEL; WI-38 (a diploid cell line), HEL, and HEC (two nontransformed human embryonic cell lines) did not form syncytia. These results indicate that SSV-I/SSAV-I forms syncytia in a variety of human transformed cells and does not always require the RSV genome for syncytia formation. (16 refs)

79-7005 Squirrel Monkey Retrovirus and *Herpesvirus saimiri*: Observation in the Same Cell Following Isolation. (Eng) Smith, G. C. (Microbiology and Infectious Diseases, Southwest Foundation Res. and Education, P.O. Box 28147, 8848 West Commerce St., San Antonio, TX 78284); Heberling, R. L.; Barker, S. T.; Kalter, S. S. *J Natl Cancer Inst* 63(4): 983-986; 1979.

The isolation of squirrel monkey retrovirus (SMRV) and *Herpesvirus saimiri* (HVS) in a mink lung cell culture previously inoculated with a squirrel monkey (*Saimiri sclerous*) throat swab suspension. HVS was identified by serum neutralization, and the retrovirus isolate was identified as SMRV by morphologic examination, microimmunodiffusion analysis, and demonstration of an Mg^{2+} preference for the RNA-directed DNA polymerase. (25 refs)

79-7006 Oligoribonucleotide Initiators for Herpes Simplex Virus DNA Synthesis In Vivo and In Vitro. (Eng) Muller, W. E. (Institut für Physiologische Chemie der Universität, Duesbergweg, 6500 Mainz, W. Germany); Zahn, R. K.; Arendes, J.; Falke, D. *Virology* 98(1): 200-210; 1979.

Experiments were carried out to determine the manner in which herpes simplex virus (HSV) DNA replication is initiated. Replicating HSV DNA, labeled with $[^3H]$ thymidine or $[^3H]$ uridine, was isolated from infected primary rabbit kidney cells. It was demonstrated that nascent DNA strands were covalently linked to oligoribonucleotide stretches. The chain length of this RNA segment was approx 36 nucleotides, which were located at the terminus of the replicating DNA. The extent of RNA initiator synthesis seemed to be closely correlated with the rate of HSV-DNA synthesis. The half-life of the RNA initiator was estimated to be 35 min. Evidence supporting the idea that cordycepin (3'-dAdo) is an inhibitor of RNA initiator synthesis included: (1) identical maximal chain length of the 3'-dAMP-RNA, (2) identical half-life of the 3'-dAMP-RNA segment, and (3) susceptibility to ribonucleases and alkali. The 3'-dAMP-RNA segment was not covalently linked to HSV-DNA. HSV-induced DNA polymerases

utilized not only deoxyribonucleotides $[d(pA)]_n$ but also ribonucleotides $[r(pA)]_n$ as initiators for the DNA template-dependent DNA polymerization. The initiating activity of both the DNA and the RNA segment was abolished when it carried a 3'-dAMP moiety at its 3'-terminus. (43 refs)

79-7007 Development of Tumours in Mice Chronically Infected with Herpes Simplex Virus. (Eng) Barinsky, I. F. (D. I. Ivanovsky Inst. Virology, USSR Acad. Medical Sciences, 123098 Moscow, USSR); Spynu, K. I.; Talalaeva, A. F.; Vanag, K. A. *Acta Virol (Praha)* 23(5): 367-374; 1979.

The oncogenicity of herpes simplex virus (HSV) in mice with chronic herpetic infections (induced by id inoculation followed by superinfection with HSV in normal or immunosuppressed animals) was studied. Within the first 10-14 days after inoculation, 20% of the mice infected with the L_2 strain of HSV type 1 and 25% of those infected with the 333 strain of HSV type 2 died of herpes infection. Neoplasms appeared 150-180 days after inoculation in 60% of the surviving mice infected with the L_2 strain and 20% of the surviving mice infected with the 333 strain. In the first group, 20/39 mice had round dense tumors in the area of the salivary glands; these mice also had tumors in the lungs and livers. The remaining 19 mice had tumors in the area of the cervical and axillary lymph nodes. Mice infected with strain 333 had similar tumors in the lymph nodes. Histologically, the tumors were adenocarcinomas and malignant lymphomas in L_2 -infected mice, and those in 333-infected mice were lymphomas and angio- or fibrosarcomas. No tumors were found at the site of HSV inoculation. HSV and Gross murine leukemia virus antigens were detected in the tumor cells, and HSV antigen was detected in cultures of tumor cells and in brain, spinal cord, liver, and spleen cells. HSV antibody was demonstrated in the sera of chronically infected tumor-bearing mice (titer = 32). (21 refs)

79-7008 Cervical Cancer Cell Lines Containing Herpesvirus Markers. (Eng) Melnick, J. L. (Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX 77030); Adam, E.; Lewis, R.; Kaufman, R. H. *Intervirology* 12(2): 111-114; 1979.

Five epithelioid cell lines were established from invasive cervical carcinoma tissue and were examined for herpes simplex virus (HSV) antigens or virus-induced changes. Immunofluorescence studies with antiserum to an HSV type 2 nonstructural polypeptide revealed perinuclear antigens. In these cell lines, concentrations of a membrane fucoprotein that is regularly present in normal cells were reduced to levels similar to those previously observed in virus-transformed cells. One of the cell lines inoculated into athymic mice produced tumors. (17 refs)

79-7009 Proteins of Herpesvirus Type 2. V. Isolation and Immunologic Characterization of Two Viral Proteins in a Virus-specific Antigenic Fraction. (Eng) Smith, C. C. (Div. Comparative Medicine, Dept. Biochemistry and Biophysics, Johns Hopkins Medical Inst., 720 Rutland Ave., Baltimore, MD 21205); Aurelian, L. *Virology* 98(1): 255-260; 1979.

AG-e, a type-common herpes simplex virus (HSV) antigen, was isolated from soluble antigenic mixtures (SAM), and its immunogenic proteins were characterized. Immunoprecipitates

resulting from the reaction of extracts of HSV-2 (G)-infected HEP-2 cells, labeled with L -[35 S]methionine 4-16 hr after infection, with anti-crude AG-e sera and antiglobulin were dissociated and electrophoresed on 8.5% sodium dodecyl sulfate (SDS)-acrylamide gels. Two proteins with electrophoretic mobilities of ICP 12 and ICP 14 and comigrating with virion proteins VP5 and VP6, respectively, were resolved in the precipitates. In another experiment, agarose segments containing the precipitin band from the crossed immunoelectrophoresis (CIE) of HSV-2 (G) SAM and anti-crude AG-e sera were dissociated and electrophoresed with results similar to those of the first experiment. The immunologic reactivity of the antisera to pure AG-e, ICP 12, and ICP 14 was studied in four assays: CIE, immunodiffusion, indirect immunofluorescence, and antiglobulin-enhanced neutralization. The reactivity of all three antisera was virus-specific in these assays. The virus neutralizing potential of the anti-ICP 12 and ICP 14 sera and the observation that their reactivity is absorbed with HSV-2 (G) virions are consistent with the comigration of ICP 12 and ICP 14 with the two virion proteins, VP 5 and VP 6. The data indicate that ICP 12 and ICP 14 are radiochemically homogeneous on SDS-acrylamide gel electrophoresis and suggest that ICP 12 and ICP 14 are virus envelope proteins. (17 refs)

- 79-7010 Cytomegalovirus Infection of Ovarian Thecoma (Letter to Editor). (Eng) LiVolsi, V. A. (New Haven, CT); Merino, M. J. *Arch Pathol Lab Med* 103(12): 653-654; 1979.

The occurrence of cytomegalovirus involving an ovarian thecoma is reported. The patient, a 61-yr-old woman, developed angioimmunoblastic lymphadenopathy following an allergic response to quinidine, which was given for cardiac arrhythmias. Postmortem examination 18 mo later revealed a malignant lymphoma with features of immunoblastic B-cell sarcoma involving lymph nodes, lungs, and bone marrow. Invasive gastrointestinal candidiasis, cytomegalovirus pneumonia, and an encapsulated nodule resembling a fibrothecoma on the right ovary were also found. Ultrastructural examination of the nodule revealed viral capsids resembling those of the herpesvirus group. Several episodes of cutaneous herpesvirus infection had been documented in this patient, and it is possible that the pulmonary and ovarian manifestations of infection observed at autopsy represented reactivation of a latent viral infection. (6 refs)

- 79-7011 Effect of Diethylstilbestrol on Replication and Transformation by Human Herpesviruses. (Eng) Rapp, F. (Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Turner, N. *Intervirology* 12(2): 103-110; 1979.

Human embryo fibroblasts treated with diethylstilbestrol (DES) gave rise to slightly increased plaque production by cytomegalovirus (CMV); plaques were also slightly larger in treated cells as compared to those in untreated cultures. There was no significant enhancement of plaque production by herpes simplex virus (HSV) types 1 and 2 in the human cells or in primary rabbit kidney cells treated with DES. Growth analyses of HSV and CMV in DES-treated cells failed to reveal enhancement of virus production when compared to untreated cells. The frequency of biochemical transformation of mouse cells deficient in thymidine kinase (TK) to the TK⁺ phenotype by HSV was markedly enhanced when cells were pretreated with DES. TK⁺-transformed colonies arising from DES-treated cells were also larger than those derived from untreated cultures. These data reveal that DES increases

susceptibility of human cell lines to CMV infection and enhances efficiency of biochemical transformation of mouse cells by HSV. (43 refs)

- 79-7012 Cytomegalovirus Isolations from Cell Cultures of Human Adenocarcinomas of the Colon. (Eng) Hashiro, G. M. (Cell Culture Lab., Cancer Res. Center, Dept. Microbiology, Univ. Hawaii, Honolulu, HI 96822); Horikami, S.; Loh, P. C. *Intervirology* 12(2): 84-88; 1979.

Cytomegalovirus was isolated from cell cultures derived from 3 of 16 surgical specimens of colonic adenocarcinoma. The patients, a 34-yr-old male, a 76-yr-old female, and a 56-yr-old male, had metastatic lesions of the descending, sigmoid, and rectosigmoid colon, respectively. Cell cultures consisted of rapidly growing fibroblastic cells. Virus identification was accomplished through electron microscopic, cytochemical, and immunofluorescent procedures. Data did not indicate an etiologic association between virus infection and cancer; however, further studies of this association are indicated. (16 refs)

- 79-7013 Further Studies of Antibody Levels to *Herpes simplex* Virus, Cytomegalovirus, Measles Virus, and Adenovirus Type 5 in Burkitt's Lymphoma Patients. (Eng) Geser, A. (Unit Biological Carcinogenesis, International Agency Res. on Cancer, 150, cours Albert Thomas, 69372 Lyon, France); Feorino, P. M.; Sohler, R. *Med Microbiol Immunol (Berl)* 167(3): 175-180; 1979.

Sera collected from 14 Ugandan Burkitt's lymphoma (BL) patients before and after tumor manifestation and from 16 BL patients only after tumor diagnosis were tested for antibodies to herpes simplex virus (HSV), cytomegalovirus (CMV), measles virus, and adenovirus type 5 (Ad 5). Immunofluorescent techniques were used for all viruses except the measles virus, which was assayed using the complement fixation technique. For anti-HSV, anti-Ad 5, and anti-CMV activities, both the prevalence of positive antibody titers (≥ 10) and the geometric mean titer of the positives varied very little between BL cases and controls both before and after diagnosis; none of the differences were significant. The antibody response to measles virus appeared to be depressed in BL patients. Similar results were obtained in the 16 children for whom only one sera (post-tumor diagnosis) was available. These results conflict with a previously published report which found elevated antibody titers to Epstein-Barr virus (EBV) and also to CMV and varicella zoster virus in BL patients. The present results fail to confirm elevation of viral antibodies in BL patients other than those to EBV; the unique relationship between this virus and BL supports the notion of etiologic involvement. (7 refs)

- 79-7014 Deoxyribonuclease Activity Found in Epstein-Barr Virus Producing Lymphoblastoid Cells. (Eng) Clough, W. (Molecular Biology Div., Univ. Southern California, Los Angeles, CA 90007). *Biochemistry* 18(21): 4517-4521; 1979.

A deoxyribonuclease (DNase) activity that is not present in B cell lines that do not undergo Epstein-Barr virus (EBV) production or in virus-negative lymphocyte cell lines was detected in EBV-producer cell lines and characterized. The nuclease was purified 220-fold, with 20% recovery. It copurified through DEAE cellulose column chromatography with the EBV-induced DNA

polymerase in EBV producer cells but eluted as a separate peak of activity on phosphocellulose chromatography. The DNase activity had a sedimentation coefficient of 4.0S, a strong divalent cation requirement, an alkaline pH optimum, and the ability to use both native and denatured lymphocyte DNA as substrate, reducing both to monophosphonucleosides. The presence of this EBV-associated enzymatic activity in cells that are undergoing active EBV DNA replication suggests that it plays an important role in the viral DNA replicative process. (18 refs)

- 79-7015** Establishment of Anti-TNP Antibody-producing Human Lymphoid Lines by Preselection for Hapten Binding Followed by EBV Transformation. (Eng) Kozbor, D. (Dept. Tumour Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden); Steinitz, M.; Klein, G.; Koskimies, S.; Makela, O. *Scand J Immunol* 10(3): 187-194; 1979.

The establishment of human lymphoblastoid cell lines producing specific antibody against the hapten trinitrophenyl (TNP) was accomplished through selection of TNP-binding human B lymphocytes by TNP-rosetting and Ficoll-Isopaque separation, followed by Epstein-Barr virus (EBV) immortalization. Derived lines secreted polyclonal anti-TNP antibodies and contained relatively small numbers of specific rosette- and plaque-forming cells against TNP-RBC. Following rosetting with TNP-RBC, the frequency of rosette-forming cells increased from 2% to 75%. In parallel, the frequency of plaque-forming cells increased from 0.4% to 30%. The antibody titers in the supernatants increased from 64 to 512 and from 48 to 192, as measured by TNP agglutination and hemolytic assays, respectively. The antibodies were 19S, IgM. The specificity of the anti-TNP antibody was confirmed by the hapten inhibition test, in comparison and cross-reactivity tests with the supernatant of the previously established, EBV-transformed anti-4-hydroxy-3,5-dinitrophenacetic acid (NNP) antibody-producing cell line. Both antibodies were specific: the homologous hapten inhibited them but the heterologous hapten did not. (22 refs)

- 79-7016** Identification of Transcribed Regions of Epstein-Barr Virus DNA in Burkitt Lymphoma-derived Cells. (Eng) Rymo, L. (Dept. Clinical Chemistry, Univ. Gothenburg, Sahlgren's Hosp., S-413 45 Gothenburg, Sweden). *J Virol* 32(1): 8-18; 1979.

RNA extracted from the Burkitt lymphoma-derived cell line Raji and from Burkitt lymphoma tumor biopsies was labeled in vitro with ³²P and hybridized to electrophoretically separated restriction endonuclease fragments of Epstein-Barr virus DNA on nitrocellulose membranes. Only certain parts of the Epstein-Barr virus genome were represented as polyribosomal RNA in Raji cells, with a pronounced dominance of RNA sequences complementary to a 2.0 x 10⁶-dalton segment of Epstein-Barr virus DNA located close to the left end of the viral genome. Mapping of virus-specific polyribosomal RNA sequences indicated that a minimum of three regions of the Epstein-Barr virus genome are expressed in Raji cells. Total-cell RNA preparations from five Burkitt lymphoma biopsies contained RNA sequences homologous to the same regions of Epstein-Barr virus DNA as polyribosomal RNA from Raji cells, albeit at different relative proportions. (34 refs)

- 79-7017** Effect of 12-O-Tetradecanoyl-Phorbol-13-Acetate on the Replication of Epstein-Barr Virus. I.

Characterization of Viral DNA. (Eng) Lin, J. C. (Cancer Res. Center, Univ. North Carolina, Box 3, Swing Building 217H, Chapel Hill, NC 27514); Shaw, J. E.; Smith, M. C.; Pagano, J. S. *Virology* 99(1): 183-187; 1979.

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) induced replication of Epstein-Barr virus (EBV) DNA in the virus-producing human lymphoblastoid cell line P3HR-1 but not in nonproducer Raji cells. A sixfold increase in EBV genome copies per P3HR-1 cell paralleled the increase in percentage of cells synthesizing viral capsid antigen. In situ cytohybridization with EBV-specific complementary RNA showed that most of the TPA-treated population participates in the virus-producing cycle. In Raji cells, abortive induction occurred, with an increase in cells showing early antigen from <0.01% to approx 10%; but no increase was seen in EBV genome copies per cell. The optimal TPA concentration for induction of viral DNA replication was 10 nanograms/ml. EBV DNA synthesized in Raji cells superinfected by virus prepared from TPA-induced P3HR-1 cells increased approx 15-fold above that of Raji cells superinfected with control virus. The buoyant densities of EBV DNA isolated from virus from TPA-induced cells or of DNA from Raji cells superinfected with TPA-induced and control virus were identical; viral DNA from all sources had the same S value. The *Xho*I restriction endonuclease digestion patterns of TPA-induced viral DNA and control viral DNA were the same as the viral DNA recovered from Raji cells superinfected with TPA-induced and control virus. Some differences were noted in the molar ratios of some of the fragments. (15 refs)

- 79-7018** EBV-Specific Humoral Antibodies in Nasopharyngeal Carcinoma Patients in Cuba. (Eng) Ruiz, R. (Inst. Oncology and Radiobiology, MINSAP, Havana, Cuba); Gurtsevich, V.; Le Riverend, E. *Neoplasma* 26(2): 125-131; 1979.

Sera of 24 Cuban patients with nasopharyngeal carcinoma (NPC) and of 60 healthy donors were studied for IgG and IgA antibodies against antigens induced by Epstein-Barr virus (EBV). Forty-three healthy subjects and all 24 cancer patients showed IgG antibodies to EBV viral capsid antigen (VCA). However, high antibody titers ($\geq 1:160$) were observed more frequently among the patients (20/24) than among the healthy donors (9/60). All but one of the NPC patients had antibodies to EBV early antigen (EA), 21 had elevated titers ($\geq 1:40$). Antibodies to EA were present in 12 healthy persons, but none had elevated titers. Sera of healthy persons were negative for antibodies against the D component of EA, while the sera of 18 NPC patients were positive, and those of 14 showed elevated titers ($\geq 1:40$). Eighteen patients had IgA antibodies against VCA, 13 against EA complex, and 3 against the D component of EA. High antibody titers ($\geq 1:20$) were found against VCA and EA in 12 and 10 patients, respectively. All but two control sera were negative for IgA antibodies. The results demonstrate that NPC in Cuba is associated with EBV. NPC patients in Cuba have higher antibody titers to EBV-associated antigens than do Caucasian patients from countries where, as in Cuba, NPC is rarely found. (32 refs)

- 79-7019** The Study of Epstein-Barr Virus Induction by Cocultivation of EBV-Transformed Cells with a Mammary Carcinoma Cell Line MCF-1. (Eng) Nyormoi, O. (International Lab. Res. Animal Diseases, P.O. Box 30709, Nairobi, Kenya). *Eur J Cancer* 15(10): 1223-1229, 1231; 1979.

Cocultivation of a human mammary carcinoma cell line, MCF-7, with various Epstein-Barr virus (EBV)-transformed cell lines resulted in virus activation. Virus production was increased by increasing the ratio of MCF-7 cells to cells of the RO-bl line in cocultivation, but EBV induction was most easily detected when cells were mixed in a 1:1 ratio. The RO-bl cells were maximally induced by the second or third day, after which the induction level declined. Another transformed cell line, B95-8, was maximally induced as early as 24 hr, and the level of induction remained high throughout the next 3 days. Although some cell lines [B95-8, Daudi, Raji, and RO-bl (a derivative of Raji)] were readily inducible, other cell lines were not [P3HR-1, EHR-B-Ramos (EBR), and JY]. EBV producers appeared to produce only early antigen (EA) and not viral capsid antigen (VCA) upon cocultivation with MCF-7. In experiments combining autoradiography and immunofluorescence it was proved that only the EBV positive cells were inducible. Heterokaryon or hybrid formation was not involved. The MCF-7 cell line had no effect upon superinfection induction of EBV antigens by non-EBV producer cells, but increased the induction by iododeoxyuridine almost threefold. Induction of EBV by MCF-7 did not follow the pattern of spontaneous EBV production nor was it induced by MCF-7-conditioned medium, thus ruling out action by a soluble diffusible substance produced by MCF-7 cells. (20 refs)

- 79-7020 Properties of Viruses Isolated from a Culture of Human Fibroblasts Treated with a Paraganglioma Filtrate. (Rus) Klenova, A. V. (N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR); Borodina, N. P.; Chizhevskaya, V. I.; Eremina, L. A.; Voskoboinik, A. D.; Shevliagin, V. Ia. *Vopr Onkol* 25(9): 42-46; 1979.

An attempt was made to characterize viruses isolated from human fibroblast cultures treated with an acellular filtrate of malignant human paraganglioma. Centrifugal analysis of purified virus preparations from transformed fibroblast cultures revealed the presence of a DNA-containing virus with buoyant density of 1.24-1.28 g/ml and an RNA-containing virus with buoyant density of 1.16-1.18 g/ml. The RNA-containing virus had no hemagglutinating activity and did not induce tumors in newborn Syrian hamsters; the DNA-containing virus, which had the properties of a papova virus, was tumorigenic in the hamsters and caused destructive changes in rat and murine embryo cultures and monkey kidney cell cultures. (10 refs)

- 79-7021 Construction and Analysis of Viable Deletion Mutants of Polyoma Virus. (Eng) Magnusson, G. (Dept. Biochemistry, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Berg, P. *J Virol* 32(2): 523-529; 1979.

Viable polyoma virus mutants with small deletions ranging in size from 2-75 base pairs were obtained by infecting 3T3 cells with polyoma DNA that had been cleaved once with *Hae*II endonuclease or with DNase-Mn²⁺ digestion. The *Hae*II endonuclease-cleaved DNA yielded mutants with deletions at map position 72-73, while the mutants generated by DNase I-Mn²⁺ digestion had deletions either at map position 72-73 or within the map coordinates 92 and 99. Both groups of mutants appeared to grow as well as wild-type virus in 3T3 cells. The deletions at map position 72-73 did not alter transforming ability of the virus in rat cells; thus, the region just to the early side of the origin of DNA replication does not appear essential for vegetative growth or transformation. However, mutants with deletions in the region

between map coordinates 92 and 99, a segment thought to code for polyoma large and middle T antigens, transformed rat cells at only 0.2 to 0.05 the efficiency of wild-type virus. (36 refs)

- 79-7022 Secondary Structures in Polyoma DNA. (Eng) Wu, M. (Dept. Chemistry, California Inst. Technology, Pasadena, CA 91125); Manor, H.; Davidson, N. *J Virol* 32(1): 334-338; 1979.

The following three reproducible secondary-structure features were observed on single strands of polyoma virus DNA mounted for electron microscopy by the T4 gene 32 protein technique: a hairpin fold-back extending from 92.9 ± 0.8 to 95.0 ± 0.7 map units, a small loop extending from 63.2 ± 3.1 to 68.5 ± 2.8 map units, and a big loop extending from 51.9 ± 2.3 to 68.9 ± 2.1 map units. Both loops were bounded by inverted repeat stems of length 40 ± 20 base pairs. The stem sequences around 68.5 and 68.9 of the large and small loops overlapped either partially or completely. The inverted repeat stems of the two secondary-structure loops appeared to lie in the regions of polyoma virus DNA flanking and probably very close to the sequences that are spliced out in the formation of the late 16S and 18S messages, whereas the hairpin fold-back appeared to map at a splicing point of an early message. These structures may therefore be important for the processing of the primary transcripts to form the early and late messages. (6 refs)

- 79-7023 Deletion Mutants of Polyoma Virus Defining a Nonessential Region Between the Origin of Replication and the Initiation Codon for Early Proteins. (Eng) Bendig, M. (Dept. Biological Chemistry, Univ. Michigan, Ann Arbor, MI 48109); Folk, W. R. *J Virol* 32(2): 530-535; 1979.

Polyoma virus mutants with deletions as large as 90 base pairs were isolated by selecting spontaneously arising genomes resistant to endonuclease *Hae*II or by treating *Hae*II- or *Bgl*-cleaved linear DNA's with S1 nuclease and exonuclease III. All of the mutants were viable, indicating that a nonessential region in the polyoma genome exists between the origin of DNA replication and the initiation codon for translation of early proteins. Several mutants with large deletions had altered growth properties, with smaller plaques and lower virus yields than the parental wild-type virus. These viruses may lack sites that are important for DNA replication or for transcription and translation of early messenger RNA's. All of the mutants tested were able to transform BHK-21 cells to anchorage independence. (38 refs)

- 79-7024 Polyoma Virus. The Early Region and Its T-Antigens. (Eng) Soeda, E. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England); Arrand, J. R.; Griffin, B. E. *Nucleic Acids Res* 7(4): 839-857; 1979.

Characterization of the DNA sequence of the early coding region of polyoma virus showed it to consist of 2,739 nucleotides. The sequence predicts that more than one reading frame can be used to code for the three known polyoma virus early proteins (designated small, middle, and large T-antigens). From the DNA sequence, the 'splicing' signals used in the processing of viral RNA to functional messenger RNAs can be predicted along with the sizes and sequences of the three proteins. Other unusual aspects of the DNA sequence were noted, including the presence of the sequence

AATAAA twice within the early region (both the signal and termination codons on both DNA strands). The DNA sequences and the predicted amino acid sequences of the respective large T-antigens of polyoma virus and the related simian virus 40 were compared, and both notable sequence similarities and differences within the early regions of these viruses were found. (36 refs)

- 79-7025 Differential Adsorption of Polyoma Virions and Capsids to Mouse Kidney Cells and Guinea Pig Erythrocytes. (Eng) Bolen, J. B. (Section Virology and Oncology, Div. Biology, Kansas State Univ., Manhattan, KS 66506); Consigli, R. A. *J Virol* 32(2): 679-683; 1979.

Surface adsorption of ^{125}I -labeled polyoma virions and capsids was examined in mouse kidney cells (MKC) and guinea pig erythrocytes (GP-RBC). Purified polyoma capsids, while lacking the ability to compete with polyoma virions for specific binding sites on the surface of MKC, were nevertheless able to block virion adsorption to GP-RBC. UV-inactivated virions blocked cellular receptors on MKC and thus inhibited virion infection of the cells. Capsids were unable to inhibit virion infection of MKC. Adsorption of polyoma virions to MKC and infection of these cells were independent of the ability of the virions to agglutinate GP-RBC. (17 refs)

- 79-7026 Isolation and Characterization of Polyoma Virus Genomes with Deletion Between the Origin of Viral DNA Replication and the Site of Initiation of Translation in the Early Region. (Eng) Wells, R. D. (Dept. Biochemistry, Univ. Wisconsin, Madison, WI 53706); Hutchinson, M. A.; Eckhart, W. *J Virol* 32(2): 517-522; 1979.

Nineteen polyoma virus mutants were isolated after treatment of isolated viral DNA with *Hae*III and S1 nuclease and infection of 3T6 cultures in a plaque assay. Electrophoresis analysis of the *Hpa*III digestion fragments indicated that all the mutants contained deletions in *Hpa*III fragment 5, that all mutants except 51-6 lacked a *Hha*I cleavage site in the neighborhood of the *Hae*III site. Analysis of the *Hae*III digestion fragments indicated that mutants 51-2 and 51-6 had patterns indistinguishable from wild-type, and that mutants 51-8, 51-15, and 51-20 had deletions that included the *Hae*III cleavage site. All 19 mutants appeared to be competent for lytic growth and for transformation of rat F2408 cells. (26 refs)

- 79-7027 Electron Microscopic Mapping of RNA Transcribed from the Late Region of Polyoma Virus DNA. (Eng) Manor, H. (Dept. Biology, Technion-Israel Inst. Technology, Haifa, Israel); Wu, M.; Baran, N.; Davidson, N. *J Virol* 32(1): 293-303; 1979.

The polyoma virus (Py) RNA species transcribed from the L DNA strand of the 'late' region of the Py genome in Py-infected mouse cells were mapped by hybridization with specific fragments of Py DNA followed by electron microscopic visualization of the hybrids. Total cellular polyadenylated Py-specific RNA molecules having an S value in the range of 16S to 20S were purified by oligodeoxythymidylic acid-cellulose column chromatography, preparative hybridization with Py DNA, and sucrose gradient centrifugation. Cytoplasmic Py-specific RNA was purified similarly but without fractionation by sucrose gradient centrifugation.

Hybrids of these RNA molecules and Py DNA fragments were spread for electron microscopy by either the cytochrome c technique or the bacteriophage T4 gene 32 protein method. The polyadenylic acid at the 3'-end of the RNA in the hybrids was identified by labeling with simian virus 40 DNA circles to which polybromodeoxyuridylic acid tails had been covalently attached. These experiments revealed the presence of three L DNA strand transcripts in both RNA preparations. Two of these RNA molecules were found to be spliced from chains transcribed from two noncontiguous parts of the late region. The third molecule either was a continuous transcript of the entire late region or contained a splicing feature which was too small to be reliably observed. The 5'-ends of the three RNA species mapped within a region extending from 68 to 70 map units on the Py restriction endonuclease map. Each of the two spliced molecules contained a 5'-terminal leader sequence transcribed from a DNA segment with an estimated length of 60 to 110 nucleotides. The 3'-ends of the leaders mapped at 66.7 ± 1.0 and 66.4 ± 0.50 map units. In these molecules the 5'-ends of the other part (the main body) mapped at 59.4 ± 0.90 and 49.4 ± 2.0 map units, respectively. The 3'-termini of all three RNA species mapped at 24 to 25 map units. (32 refs)

- 79-7028 Further Investigations on the Antioncogenic Activity of A/PR8/34 (HON1)-Influenza Virus on Polyoma Virus Induced Tumors in Newborn Wistar Rats. (Eng) Desselberger, U. (Inst. Virology, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany); Drescher, J.; Georgii, A.; Ostertag, H. *Zentralbl Bakteriell [Orig A]* 240(4): 411-423; 1978.

The anti-oncogenic activity of influenza virus was investigated in newborn Wistar rats inoculated simultaneously with polyoma virus (Stewart Eddy strain). The rats were inoculated ip with egg-adapted A/PR8/34 (HON1) influenza virus and sc with the polyoma virus within 24 hr after birth. The kidneys were examined for tumors 40 days later. The anti-oncogenic activity of influenza virus was neutralized by the addition of homologous influenza antibodies, indicating that this activity was caused by the virus rather than by any nonviral material. Anti-oncogenic activity was critically dependent on the relative doses of both viruses (576-2,591 hemagglutinating units of polyoma virus; 106-848 hemagglutinating units of influenza virus) and declined with storage at 4°C. Influenza virus significantly reduced antibody responses to polyoma virus in all experiments, suggesting that influenza virus reduced the multiplication of polyoma virus. Conversely, polyoma virus significantly enhanced antibody responses to influenza virus in two of six experiments. The anti-oncogenic activity of influenza virus seemed to be a result of its hemagglutinin component rather than the presence of neuraminidase. Influenza virus markedly reduced polyoma virus adsorption on rat embryo fibroblast cultures, suggesting that anti-oncogenic activity may be at least partially caused by interference with polyoma virus adsorption on target cells. (12 refs)

- 79-7029 Polyoma Virus-specific 55K Protein Isolated from Plasma Membrane of Productively Infected Cells is Virus-coded and Important for Cell Transformation. (Eng) Ito, Y. (Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London, WC2A 3PX, England). *Virology* 98(1): 261-266; 1979.

A 55,000 (55K_{PM}) mol wt protein obtained from the plasma membrane fraction of mouse cells productively infected with polyoma virus was compared with polyoma virus middle (55K mol wt) T an-

tigen. The electrophoretic mobility of 55K_{PM} from the plasma membrane fraction was indistinguishable from that of the middle T antigen from a detergent extract of unfractionated productively infected cells. Cells infected with the nontransforming polyoma virus mutant NG-18 did not express plasma membrane-associated 55K_{PM} protein or middle T antigen, which suggests that the middle T antigen and the 55K_{PM} protein are identical. More direct evidence on the identity of the proteins was obtained by peptide mapping of (35S) methionine-labeled middle T antigen and 55K_{PM}. The methionine peptides were analyzed by a two-dimensional fingerprinting technique, which showed that the fingerprint of the 55K_{PM} was similar (and probably identical) to that of middle T antigen. These results establish that the middle T antigen is associated with cell membranes. Of three membrane fractions separated so far, the 55K_{PM} protein is enriched in the plasma membrane fraction. These results suggest that the plasma membrane may be a site where at least one of the primary events of in vitro cell transformation by the virus occurs. (18 refs)

- 79-7030 Two Cases of Epidermodysplasia Verruciformis with Malignant Changes. (Jpn) Miyachi, Y. (Dept. Dermatology, Faculty Medicine, Kyoto Univ., Kyoto, Japan); Oguchi, M.; Ogino, A.; Komura, J.; Uehara, M.; Nikaido, M. *Hifuka Kiyo* 74(1/2): 29-35; 1979.

The cases of a 27-yr-old man and a 24-yr-old man with epidermodysplasia verruciformis that underwent malignant changes are reported. The parents of both patients were cousins, but neither family had histories of the same diseases. The first patient had human leukocyte antigens A9, --B12, and BW54 and the second patient had A2, A9, BW52--. Histological examination of the first patient's tumor showed translucent cells with a granulocytic layer, a brush-border cell layer, and small round cell infiltration of the papillary epithelial layer. The second patient had squamous cell carcinoma cells with mitotic patterns. Both tumors were resected surgically. Because some cellular immunity tests were depressed, it was thought that hereditary or immunological defects may have accounted for the absence of the spontaneous regression phenomenon seen in plane warts. (21 refs)

- 79-7031 BK Virus DNA: Complete Nucleotide Sequence of a Human Tumor Virus. (Eng) Yang, R. C. (Section Biochemistry, Molecular and Cell Biology, Cornell Univ., Ithaca, NY 14853); Wu, R. *Science* 206(4417): 456-462; 1979.

The complete DNA sequence of the human papovavirus BK is presented. From the 4963 base-pair sequence of BK virus (MM strain), the amino acid sequence of at least five proteins can be deduced: a T antigen and a t antigen, which share amino terminal peptides; proteins VP2 and VP3, which share 232 amino acids; and protein VP1, whose coding sequence overlaps those for VP2 and VP3 by 113 nucleotides but is read in a different frame. The gene loci and the arrangement of genes are strikingly similar in BK virus and simian virus 40 (SV40). The sequence of the deduced proteins in BK virus shares 73% amino acid homology with those in SV40, while the DNA sequence of the two viruses shares 70% homology, suggesting a close evolutionary relationship. However, the repeated DNA sequences in the noncoding regions of these viruses are different. (39 refs)

- 79-7032 Helper Function for Adenovirus Replication in Monkey Cells by BK Human Papovavirus. (Eng) Miyamura, T. (Natl. Inst. Allergy and Infectious Diseases, NIH,

Bethesda, MD 20205); Takemoto, K. K. *Virology* 98(1): 279-282; 1979.

Experiments were carried out to study the growth of BK human papovavirus (BKV) in CV-1 monkey kidney cells at the permissive temperature (40 C) and at 37 C. At 37 C, all infected cells synthesized T antigen, but <5% of the cells produced viral antigen. When infected cells were incubated at 40 C, characteristic cytopathic effects (CPE) were observed with high virus yields. The inhibition of BKV growth in CV-1 cells was thus shown to be a temperature-dependent phenomenon. Experiments were then conducted to determine whether BKV provides a helper function for adenovirus >growth in CV-1 cells at temperatures that were either permissive (40 C) or semipermissive (37 C) for BKV replication. At 37 C, there was a low level of adenovirus enhancement of 0.5 to 1.0 log increase. However, at 40 C, there was a 1.5 to 2.5 log increase in adenovirus yields, comparable to those obtained by coinfection with simian virus 40 (SV40) and adenovirus. These data provide additional information on common viral functions shared by BKV and SV40. (27 refs)

- 79-7033 Perinatal Induction of Medulloblastomas in Syrian Golden Hamsters by a Human Polyoma Virus (JC). (Eng) Zu Rhein, G. M. (Dept. Pathology, Univ. Wisconsin Medical Center, Madison, WI 53706); Varakis, J. N. *Natl Cancer Inst Monogr* (51): 205-208; 1979.

Outbred Syrian hamsters (*Mesocricetus auratus*) developed one or more malignant medulloblastomas 3-6 mo after they were inoculated as newborns intracerebrally and sc with JC virus, a papovavirus originally isolated from a human with progressive multifocal leukoencephalopathy. About 95% of the tumor-bearing animals had at least one neoplasm of the cerebellum that corresponded in location and morphology to the human medulloblastoma of childhood. Hamster tumors were located either in the vermis or in one hemisphere, and were about 5 mm wide. The tumors originated from cells of the internal granular layer (IGL) of the cerebellum. The first atypical IGL cell appeared from 4-8 wk after inoculation, and incipient tumors were visible at 10 wk. Virus was isolated from five of seven hamster medulloblastomas. The JC virus was the first infectious agent to produce this neoplasm in any species. It is hypothesized that upon injection, the virus spreads over the brain surface, infecting the mitotically active cells still on the surface in the external granular layer. The viral genome incorporates into the cellular genome, and the cells transform. Later, the transformed cells migrate to the IGL, and, under the influence of unknown factors, the transformation is subsequently expressed phenotypically. (8 refs)

- 79-7034 Characterization of Different Tumor Antigens Present in Cells Transformed by Simian Virus 40. (Eng) Smith, A. E. (Translation Lab., Imperial Cancer Res. Fund, London WC2A 3PX, England); Smith, R.; Paucha, E. *Cell* 18(2): 335-346; 1979.

Different forms of tumor antigen (T-ag) present in a number of simian virus 40 (SV40)-transformed cell lines were analyzed by tryptic peptide fingerprinting and by cell-free synthesis. Fingerprint analysis showed that nonviral tumor antigens (NVT-Ags) had few if any peptides in common with large T antigens or small t antigens, and that they lacked the amino terminal tryptic peptide and the peptides unique to small t. NVT-Ags from different species had different fingerprints, but those isolated from different

transformants of the same cell line were identical. The size of NVT was unaltered in cells transformed by mutants of SV40 with deletions in the region 0.60-0.55 map units. The messenger RNA for NVT did not hybridize to SV40 DNA. The other forms of T-Ag isolated from transformed cells fell into three classes: shortened forms of large T (truncated large T); multiple species of T-Ag with mol wt very similar to, but distinct from, those of normal large T (large T doublets and triplets); and elongated forms of large T (super T). These proteins all contained the normal amino terminus of SV40 T-Ags, and the truncated forms of large T lacked peptides from the carboxy terminal half of large T. One species of super T (mol wt 130,000) contained only those methionine tryptic peptides present in normal large T, although it may contain some peptides in more than one copy. (46 refs)

- 79-7035 Subculture Requirement for Rescue of SV40 from 'Nonrescuable' Cell Lines. (Eng) Moyer, M. P. (Thor- man Cancer Res. Lab., Trinity Univ., San Antonio, TX 78284); Moyer, R. C. *Intervirology* 12(2): 89-95; 1979.

A variety of cell lines that had not previously yielded virus after fusion with permissive cells were used in experiments to determine whether simian virus 40 (SV40) could be rescued following extensive subculture and assessment of virus rescue. After cell fusion with permissive TC7 cells, SV40 could be rescued from the H50, BRKSV (Bam 1 linear), 14B, and 14B (1-4) cell lines, all of which contain the entire SV40 genome. Virus could not be rescued from the T22 cell line, which was transformed by defective virus. The T-antigen-negative flat revertant cell line 14B (1-4) converted to T-antigen-positive prior to virus rescue. Subculture and extensive monitoring for production of infectious virus appeared to be prerequisites for the detection of virus rescue. These studies suggest that previously reported negative results for rescue of other viruses, such as polyoma and adenovirus, should be reevaluated. (14 refs)

- 79-7036 Oncogenicity of Simian Virus 40 Deletion Mutants that Induce Altered 17-Kilodalton t-Proteins. (Eng) Lewis, A. M. (Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD 20205); Martin, R. G. *Proc Natl Acad Sci USA* 76(9): 4299-4302; 1979.

Plaque-purified viable simian virus 40 (SV40) deletion mutants containing deletions between map positions 0.54 and 0.59 induced tumors in 21-92% of LSH hamsters inoculated during the first 24 hr of life. *HinfI* restriction endonuclease digestion patterns of the genomes of virions rescued from the tumor cells and the distribution of SV40 early proteins in these cells indicated the association of tumor induction with the inoculated mutants. These results imply that the DNA sequences comprising that portion of the early SV40 genome between map positions 0.54 and 0.59 are not essential for SV40 oncogenicity. (20 refs)

- 79-7037 Isolation of a SV40-like Papovavirus From a Human Glioblastoma. (Eng) Scherneck, S. (Central Inst. Molecular Biology, 1115 Berlin-Buch, W. Germany); Rudolph, M.; Geissler, E.; Vogel, F.; Lubbe, L.; Wahlte, H.; Nisch, G.; Weickmann, F.; Zimmermann, W. *Int J Cancer* 24(5): 523-531; 1979.

Indirect immunofluorescence staining of a human glioblastoma multiforme (M27) tested in early cell cultures showed Simian virus 40 (SV40)-related tumor (T)-antigen in 95% of the cells. SV40-related viral capsid (V)-antigen was absent in all cells tested. Virus rescue was performed by fusing M27 cells with SV40-permissive CV-1 monkey cells by using polyethylene glycol as fusion factor. Virus particles were isolated from the glioblastoma multiforme and termed SV40-GBM. Electron microscopy showed that the SV40-GBM particles correspond in size and morphology to papovaviruses. Serological tests (hemagglutination, neutralization, fluorescent antibody) revealed that the virus is indistinguishable from SV40; nevertheless, SV40-GBM did appear to differ slightly from the SV40 wild type. SV40-GBM could propagate and produce a cytopathic effect in both CV-1 cells and primary fetal human kidney cells. Digestion of SV40-GBM DNA with the *HindIII* restriction endonucleases revealed minor differences compared with SV40 DNA. (36 refs)

- 79-7038 The SV40 A Gene Product is Required for the Production of a 54,000 MW Cellular Tumor Antigen. (Eng) Linzer, D. I. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ 08540); Maltzman, W.; Levine, A. J. *Virology* 98(2): 308-318; 1979.

Experiments were carried out to determine whether a 54,000 mol wt protein that is specifically immunoprecipitated from simian virus 40 (SV40)-infected and -transformed mouse cells is also present in uninfected Balb/c 3T3 cells and to further characterize the protein. It was demonstrated that low levels of a 54,000 mol wt protein are present in uninfected, nontransformed mouse 3T3 cells. Following infection or transformation of 3T3 cells with SV40, the levels of this protein increased 25- to 50-fold. In SV40-infected 3T3 cells, the rate of synthesis of the viral 94,000 mol wt T antigen increased over the first 14 hr after infection and then declined. In contrast, the rate of synthesis and/or the stability of the 54,000 mol wt protein increased over a 22-hr period and then remained at max levels for an additional 30 hr. Temperature-sensitive A gene mutants of the SV40 large T antigen, at the nonpermissive temperature, failed to initiate or maintain the max increased levels of 54,000 mol wt protein observed in virus-infected or -transformed cells. SV40 deletion mutants in the small t antigen unique region of the genome stimulated the production of wild-type levels of the protein in virus-infected cells. The results demonstrate that the SV40 A gene product is required to initiate and possibly maintain the high levels of the 54,000 mol wt protein found in virus-infected and -transformed cells. (19 refs)

- 79-7039 Detection of Simian Virus 40 Related T-Antigen in Human Meningiomas. (Eng) Scherneck, S. (Abteilung Zellgenetik, Zentralinstitut für Molekularbiologie, Akademie der Wissenschaften der DDR, Lindenberger Weg 70, DDR-115 Berlin-Buch, E. Germany); Lubbe, L.; Geissler, E.; Nisch, G.; Rudolph, M.; Wahlte, H.; Weickmann, F.; Zimmermann, W. *Zentralbl Neurochir* 40(2): 121-127, 129-130; 1979.

Indirect immunofluorescence testing of 37 human primary meningiomas in cell culture revealed the 12 expressed simian virus 40 (SV40)-related-tumor (T)-antigen. In at least one case, treatment of the patients with SV40-containing polio vaccine was excluded. The percentage of T-antigen-positive nuclei varied between 20% and 95%. There was a decrease in T-antigen-positive cells in the same tumor culture with increasing passage. The T-antigen was granular and filled the whole nucleus. None of the meningioma

cell cultures tested showed SV40-related V-antigen, nor could infectious virus be visualized by electron microscopy. The presence of SV40 T-antigen could not be correlated with the sex or age of the patients, nor with the histological or chromosomal characteristics of the meningioma. These findings indicate that early functions of a papovavirus-like particle are expressed in the meningiomas: this particle shares at least some of the antigenic properties of SV40. (23 refs)

- 79-7040** Comparison of Simian Virus 40-induced Mouse and Hamster Tumor-specific Transplantation Antigens. (Eng) Coggin, J. H. (Dept. Microbiology and Immunology, Coll. Medicine, Univ. South Alabama, Mobile, AL 36688). *J Natl Cancer Inst* 63(4): 1029-1034; 1979.

The tumor-specific transplantation antigens (TSTA) of mouse and hamster tumor cells induced in vivo by simian virus 40 (SV40) were compared. TSTA extracted from SV40-induced mouse sarcoma cells and from intact irradiated mouse sarcoma cells did not prevent SV40 oncogenesis or tumor take following transplantation in LVG strain Syrian hamsters, but they did prevent tumor take following specific tumor transplantation in BALB/c mice. Human and hamster cells transformed by SV40 were able to interrupt SV40 oncogenesis in the hamster. Thus, the TSTA of SV40-induced mouse sarcomas did not appear to be the same as the TSTA that appear on human, rat, and hamster cells transformed by SV40. Tumor antigen may be the immunizing component that has previously been isolated from mouse sarcoma cells, or there may be a peculiar histocompatibility barrier in the hamster to the immunogenicity of TSTA induced in mouse cells. (16 refs)

- 79-7041** Sarcomas Induced by Injection of Simian Virus 40 into Neonatal CFW Mice. (Eng) Hargis, B. J. (Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA 02115); Malkiel, S. *J Natl Cancer Inst* 63(4): 965-968; 1979.

The role of malarial immunosuppression in the development of simian virus 40 (SV40)-induced tumors in mice was studied. Infection with murine malaria parasites, *Plasmodium berghei yoelii*, decreased the latency and increased the incidence and invasiveness of sarcomas induced in neonatal CFW mice by the iv injection of SV40. All mice that received both SV40 and *P. berghei yoelii* had liver and spleen sarcomas at 9 mo of age. At 11 mo of age, 70% of the SV40-inoculated mice had liver sarcomas indistinguishable from those in the group given both pathogens. Only one lung metastasis was seen in the SV40-treated group. The indirect immunofluorescence technique demonstrated the presence of SV40 T-antigen in the sarcomas. Among adult CFW mice given iv injections of SV40, only two tumors were found at 11 or 12 mo after virus inoculation. Both tumors were in the lungs; one was an adenoma and one was a papillary adenocarcinoma. Neither gave a positive reaction in the immunofluorescence test. (10 refs)

- 79-7042** Malignant Behaviour of Three Adenovirus-2-transformed Brain Cell Lines and Their Methyl Cellulose-selected Sub-clones. (Eng) Gallimore, P. H. (Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham, B15 2TJ, England); McDougall, J. K.; Chen, L. B. *Int J Cancer* 24(4): 477-484; 1979.

Three adenovirus-2-transformed rat embryo brain cell lines and their methylcellulose-selected subclones were examined for fibronectin expression, anchorage-independent growth, saturation density, T antigen expression, and morphology. Tumorigenicity studies were carried out on newborn and rabbit anti-rat thymocyte serum-immunosuppressed syngeneic rats and congenitally athymic nude mice. With one exception the methylcellulose subclones contained significantly fewer fibronectin-positive cells than did the parent lines; a number of subclones contained no fibronectin-positive cells. Methylcellulose selection did not always alter cell morphology, saturation density or anchorage-independent growth as compared with parent lines. However, the methylcellulose subclones were considerably more malignant than the parent cell lines as measured by invasion and metastasis in nude mice. No in vitro characteristic correlated with malignant behavior. (17 refs)

- 79-7043** Intercistronic Complementation Between Adenovirus 2 Temperature-sensitive Mutants. (Eng) Plaat, D. (Department de Microbiologie, Centre Hospitalier Universitaire, Universite de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada); Weber, J. *Virology* 98(1): 55-62; 1979.

The mechanism of intercistronic complementation was examined at the molecular level using well defined adenovirus type 2 temperature-sensitive (ts) mutants that map into discrete and separate regions on the adenovirus genome. In particular the synthesis of a 50K core-polypeptide, related to protein V, and the processing of core protein PVII were examined. The efficiency of complementation was unique to each mutant. Coinfection with wild-type virus failed to suppress completely the mutant phenotype, suggesting that the mutants were defective in non-catalytic proteins. Interserotype complementation between Ad2ts3, a hexon mutant, and Ad5ts22, a fiber mutant, resulted in mosaic virions with Ad2 fibers and Ad5 hexons, rather than in mosaic capsomeres. The putative hexon mutant, ts3, was found to exert a gene frequency-dependent dominance. Evidence suggesting that the ts3-specific 50K polypeptide may be a precursor to core protein V was obtained. It is concluded that complementation is profoundly influenced by the nature of the participating gene products and their function in virus infection. (26 refs)

- 79-7044** Spontaneous, Mutagen-induced and Adenovirus-induced Anchorage Independent Tumorigenic Variants of Mouse Cells. (Eng) Bellett, A. J. (Dept. Microbiology, John Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T. 2600, Australia); Younghusband, H. B. *J Cell Physiol* 101(1): 33-47; 1979.

Although normal C57 Black mouse embryo cells were not able to form colonies in agarose, rare variant (ar⁺) cell lines able to grow in agarose were established. Fluctuation analysis showed that ar⁺ variants arose by spontaneous mutation in the cultured cells. The frequency of ar⁺ variants was increased by treating cells with N-methyl-N'-nitro-N-nitrosoguanidine or ethyl methane sulfonate, or by abortive infection with human adenovirus type 5. Induced ar⁺ cells were fibroblastic; most grew slowly and had slightly reduced saturation density and increased serum requirements. Of twenty ar⁺ clones induced by Ad5, 14 were T-antigen-negative; two of these were also negative when tested for viral DNA. Six clones contained a few cells that were T-antigen-positive when first tested, but were negative when retested later. The ar⁺ variants were tumorigenic in athymic and in normal syngeneic mice. These results suggest that the ar⁺ phenotype can arise by spontaneous or

chemically induced mutation and can be induced by adenovirus through a process differing from classical transformation. (46 refs)

- 79-7045 Structure of Two Spliced mRNAs from the Transforming Region of Human Subgroup C Adenoviruses. (Eng) Perricaudet, M. (Unite de Genie Genetique, Institut Pasteur, 28 rue du Dr. Roux, 750 15 Paris, France); Akusjarvi, G.; Virtanen, A.; Pettersson, U. *Nature* 281(5733): 694-696; 1979.

Clones corresponding to the 12S and 13S messenger RNA (mRNA) from the transforming region (E1A) of human subgroup C adenoviruses were isolated and characterized by hybridization and sequence analysis. It was possible to combine sequence information from the clones with the genomic DNA sequence of adenovirus type 5 (Ad5) to deduce the structure of the 12S and 13S mRNAs from region E1A. The structure derived is based on the assumption that the 12S and 13S RNAs have common 5'- and 3'-ends. The polypeptides specified by the 13S and 12S mRNAs are predicted to be 288 and 242 amino acids long, with mol wts of 32,000 and 26,000, respectively. Both polypeptides should have identical amino- and carboxy-terminal ends, their only difference being a deletion of 46 internal amino acids from the polypeptide specified by the shorter mRNA. Both peptides should be unusually rich in proline and glutamic acid. It appears that more polypeptides have been assigned to region E1A than can be accounted for by the mRNAs observed by electron microscopy and the S₁ nuclease assay. Sequence analysis of additional clones will be required to resolve this problem. (22 refs)

- 79-7046 Tumorigenicity and Viral Gene Expression in Rat Cells Transformed by Ad 12 Virions or by *EcoRI* C Fragment of Ad 12 DNA. (Eng) Mak, S. (Dept. Biology, McMaster Univ., Hamilton, Ontario, L8S 4K1, Canada); Mak, I.; Smiley, J. R.; Graham, F. L. *Virology* 98(2): 456-460; 1979.

Several rat kidney cell lines transformed either by adenovirus 12 (Ad 12) virions or by the *EcoRI* C fragment (left 16%) of Ad 12 DNA were characterized with respect to viral DNA content, viral gene expression, and tumorigenicity. Virion-transformed cells contained viral DNA sequences from most regions of the viral genome while *EcoRI* C fragment-transformed cells contained only part of the C fragment. All cell lines transcribed DNA sequences from the left 6.7% (*HindIII* F fragment) of the genome; some lines also transcribed sequences extending into the adjacent *HindIII* H fragment. Virus-transformed and DNA-transformed lines induced tumors in immunocompetent rats with equal efficiency. (17 refs)

- 79-7047 Adenovirus Type 12 Tumor Antigen. II. Immunoprecipitation of Protein Kinase from Infected and Transformed Cells by Antisera to T Antigen and Some Normal Rat Sera. (Eng) Raska, K. (Dept. Pathology, Coll. Medicine and Dentistry, New Jersey-Rutgers Medical Sch., Piscataway, NJ 08854); Geis, A.; Fohring, B. *Virology* 99(1): 174-178; 1979.

Protein kinase was precipitated from adenovirus type 12 (Ad12)-infected KB cells and Ad12-transformed hamster cells by sera of tumor-bearing hamsters and rats. Immunoprecipitates obtained with T antigen reactive sera catalyzed transfer of ³²P from [γ -³²P]ATP to the γ -chain of IgG. In control cells, analogous products were without significant activity, and control hamster sera

did not precipitate protein kinase from infected and transformed cells. Some control rat sera (syngeneic with immune sera), however, did precipitate protein kinase from infected and transformed cells; sera of female breeder rats were particularly active. When partially purified, highly immunoreactive T antigen preparations from transformed cells were used as a source of enzymatic activity, protein kinase was detected only in precipitates obtained with immune sera. (16 refs)

- 79-7048 Tumor-specific Transplantation and Surface Antigen in Cells Transformed by the Adenovirus 12 DNA Fragments. (Eng) Shiroki, K. (Inst. Medical Science, Univ. Tokyo, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108, Japan); Shimojo, H.; Maeta, Y.; Hamada, C. *Virology* 99(1): 188-191; 1979.

Adenovirus type 12 (Ad 12) tumor-specific transplantation antigen (TSTA) and surface (S) antigen were examined in 3Y1 rat cells transformed with Ad 12 DNA and its fragments. The cells used were WY3 (3Y1 cells transformed by whole Ad 12 DNA), CY1, (3Y1 cells transformed by the *EcoRI*-C fragment of Ad 12 DNA, GY cells (3Y1 cells transformed by the *HindIII*-G fragment of Ad 12 DNA), and HY cells (3Y1 cells transformed with the *BpaI*-H-fragment of Ad 12 DNA). The transformed cells (10⁶ to 5 x 10⁶) were transplanted sc into Fischer rats 1-28 days old. Tumor incidence was significantly different between the controls and animals immunized with WY3, CY1, or GY cells but not in those immunized with the HY cells. This suggests that TSTA of Ad 12 is present in WY3, CY1, and GY1 cells but not in HY cells. Membrane immunofluorescence demonstrated S antigen in WY3, CY21, and GY cells but not in HY cells. These results show that WY3, CY1 and GY cells contain TSTA and S antigen in addition to the previously demonstrated T antigen and suggest that all of these antigens contain a protein(s) coded for by the Ad 12 transforming gene, which is located on the left end (7.2%) of the viral genome. The results also suggest that the genetic information needed for the initiation of transformation is contained in map unit 1-4.5 and that needed for maintenance of transformation in map unit 4.5-7.2. (18 refs)

- 79-7049 Development and Alternate Changes of Surface Antigen in Adenovirus Type 12-transformed Cells. (Eng) Hamada, C. (Sch. Medicine, Niigata Univ., Asahimachi 1-757, Niigata 951, Japan); Maeta, Y. *Gann Monogr Cancer Res* 23: 175-180; 1979.

A virus-specific surface (S) antigen in adenovirus type 12 (Ad12)-transformed cells underwent alternate changes in vitro and in vivo. In a fluorescent antibody test, while all of the hamster and mouse cells transformed in vitro with Ad12 were positive for the S antigen, tumor cells in vivo, produced by grafting the transformed cells, were negative [S(+) and S(-), respectively]. Conversely, the S(-) cells could be converted to S(+) by repeated subcultures in vitro or by Ad12 infection. In addition, H-2 antigens in Ad12-transformed mouse cells were no longer detectable after allografting. The various phenotypes of Ad12-transformed cells thus obtained were examined for their immunological properties. S(+) cells were more immunosensitive and less tumorigenic than S(-) cells. Coexistence of the S and H-2 antigens was required for cells to be injured by immune spleen cells. These findings are discussed from the viewpoint of tumor immunity. (15 refs)

- 79-7050 Structure and Function of Adenovirus Type 12 Defective Virions. (Eng) Mak, I. (Dept. Biology, McMaster

Univ., Hamilton, Ontario, L8S 4K1, Canada); Ezoe, H.; Mak, S. *J Virol* 32(1): 240-250; 1979.

Adenovirus type 12 preparations purified from human KB cells contained defective virions with a lighter density. The light virions were separated by banding in CsCl density gradients. Ultrastructural examination of DNA extracted from the light virions indicated that it was 3%-3.5% shorter than DNA from complete virions. Ultrastructural findings, restriction endonuclease analysis, and the results of DNA-DNA hybridization experiments indicated that about 50% of the DNA molecules from the light virions contained deletions ranging 4.5% to 8%, mapping near 16% from the left-hand end of the genome. The plaquing efficiency of the light virions was 5%-14% that of the complete virions. By the immunofluorescence technique, the light virions were shown to induce early (T-antigen) and late viral structural polypeptides (V-antigen) as efficiently as the complete virions. The light virions also induced tumors in newborn hamsters with the same efficiency as the complete virions. These results indicate that the deleted regions of the genome are not essential for late gene expression. (35 refs)

- 79-7051 In Vivo and In Vitro Biological Activity of an Oncogenic DNA Virus (Cancer Virus). (Spa) Alvarez Noves, J. (Departamento de Biología y Bioquímica de Cáncer, Instituto Nacional de Oncología, Ciudad Universitaria, Madrid-3, Spain); Alvarez Rodriguez, Y.; Valladares, Y. *Rev Esp Oncol* 25(3): 377-383; 1978.

The biological activity of an oncogenic DNA virus (cancer virus, CV) was studied in vitro in a cell line (ERGA) established from mouse embryo cells and in vivo in *Mesocricetus auratus*. The in vitro tests demonstrated cell degeneration, increased phagocytosis by the surviving cells, reduction of the mitotic activity, and the appearance of foci of cellular transformation. The transformed cells did not release virus. Golden hamsters were followed for up to 12 mo after sc injection of CV from the ERGA cell cultures; 77 of the 105 animals developed at least one tumor. Tumors included 50 multicentric fibrosarcomas of the heart, 12 polymorphous epithelial thymomas, 3 pleomorphic tubular carcinomas of the kidney, 24 polymorphocellular sarcomas of the sc tissue (usually at or near the injection site), and 2 other tumors. Most tumors were found within the first 3 mo after inoculation. (9 refs)

- 79-7052 Oncornavirus-like Particles Released by Human Prostatic Explant Cultures. (Eng) Job, L. (Dept. Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY 14263); Arya, S. K.; Carter, W. A.; Horoszewicz, J. S. *Oncology* 36(6): 248-253; 1979.

Epithelial explant cultures from several human prostatic tissues released oncornavirus-like particles. The extracellular particles, obtained from culture medium conditioned by the explants, banded at a density of 1.1-1.2 g/cm³ in a sucrose density gradient. The particles contained RNA-directed DNA polymerase that utilized poly (2'-O- (2'-O-methylcytidylic acid) as a template, and showed preference for polyadenine over poly-d-adenine and manganese over magnesium. The particles also contained RNA that directed DNA synthesis in vitro. The synthesized DNA was associated with RNA, some of which was high-mol-wt RNA. Explant cultures from 5/15 hyperplastic prostatic specimens and 3/4 prostatic adenocarcinoma specimens released particles that banded at a density of 1.1-1.2 g/cm³ and contained RNA-directed DNA

polymerase. Explant cultures from two normal prostates did not release such particles. No particles were found in the culture medium conditioned from monolayers of monkey-kidney CV-1 cells. (21 refs)

- 79-7053 Characterization of Infectious Oncornaviruses from MOPC-460 Plasmacytomas: Their Relation to A-Type Particles. (Eng) Ramabhadran, T. V. (Dept. Biology, Washington Univ., St. Louis, MO 63130); Hartley, J. W.; Rowe, W. P.; Godefroy-Colburn, T.; Jhabvala, P. S.; Thach, R. E. *J Virol* 32(1): 123-130; 1979.

MOPC-460 plasmacytoma cells grown in tissue culture produce intracellular A-type particles and closely related extracellular oncornavirus-like particles (myeloma-associated virus: MAV); an attempt was made to transmit MAV to homologous (mouse) and heterologous (mink) cells. This resulted in the isolation of ecotropic and xenotropic infectious forms of murine leukemia virus (MuLV). The relationship of these two isolates (MuLV_{eco} and MuLV_{xeno}) to A-type particles and to MAV was investigated by nucleic acid hybridization. Using complementary DNA probes prepared from MuLV_{eco} and MuLV_{xeno}, these infectious MuLV were found to differ from A-type particles and from MAV. It was also found that MAV was the predominant extracellular component; MuLV_{eco} and MuLV_{xeno} were present at low levels (<5%) in MAV preparations. Ultrastructure examination showed that neither mouse embryo cells infected with MuLV_{eco} or mink cells infected with MuLV_{xeno} contained cytoplasmic A-type particles. MuLV_{eco} and MuLV_{xeno} appear to be BALB/c endogenous viruses that are induced when MOPC-460 solid tumor cells are adapted to growth in cell culture. The inability to transfer MAV into cells permissive to MuLV of ecotropic or xenotropic host range suggests that MAV may be defective and/or noninfectious. (36 refs)

- 79-7054 Characterization of the Proteins of Intracisternal Type A and Extracellular Oncornavirus-like Particles Produced by MOPC-460 Myeloma Cells. (Eng) Robertson, D. L. (Dept. Microbiology, Univ. California, San Francisco, CA 94143); Jhabvala, P. S.; Godefroy-Colburn, T.; Thach, R. E. *J Virol* 32(1): 114-122; 1979.

The mouse plasmacytoma cell line MOPC-460 produces both intracisternal and intracytoplasmic A-type particles when grown as a solid tumor. When these cells are grown either as an ascites tumor or in tissue culture, a third type of particle is produced extracellularly. This particle, the 'myeloma-associated virus,' is closely related to, and probably an alternate form of, the intracisternal A-type particle. The proteins present in these two particles were compared by tryptic peptide mapping. Both types of particles were found to contain essentially the same major proteins of 76,000 (p76) 68,000 to 70,000 (p68-70), and 45,000 (p45) daltons as well as varying amounts of smaller proteins. The relative proportions of all these proteins varied from preparation to preparation in an unpredictable way. The p45, p68, and p70 proteins all contained sequences found in p76, suggesting precursor-product relationships of p76 to p70 to p45 for solid tumor A-type particles and p76 to p68 to p45 for extracellular myeloma-associated virus. In addition, immune precipitation experiments established that p76 contains at least some of the antigenic determinants characteristic of murine leukemia virus p30. This confirms earlier nucleic acid hybridization studies indicating a moderate degree of relatedness between MOPC-460 A-type particles and several standard murine leukemia and sarcoma viruses. Taken together, these

VIRAL CARCINOGENESIS

results provide evidence supporting the concept that MOPC-460 A-type particles may represent aberrant forms of C-type murine viruses. (47 refs)

- 79-7055 Tumorigenicity and Intracisternal A-Particle Expression of Hybrids Between Murine Myeloma and Lymphocytes. (Eng) Giacomoni, D. (Dept. Microbiology and Immunology, Univ. Illinois Medical Center, Chicago, IL 60612). *Cancer Res* 39(11): 4481-4484; 1979.

Hybrids of BALB/c lymphocytes and a murine myeloma that expresses intracisternal A-particles were obtained with polyethylene glycol as the fusogen. The karyotype, tumorigenicity, and A-particle expression of the hybrid clones were assessed. All the hybrid clones analyzed were tumorigenic and expressed intracisternal A-particles even when they were the result of a fusion event between two lymphocytes and one myeloma cell in which no loss of chromosomes was detected. The tumors that developed following inoculation of hybrid cells into BALB/c mice (1×10^6 cells/mouse) were karyotypically identical to the inoculated cells. It appears that the two myeloma cell phenotypic traits analyzed (tumorigenicity and A-particle expression) are dominant. (23 refs)

- 79-7056 In Vivo Infectivity of the Fibrotropic C-Type Viral Isolates From C57BL/Ka Mice. (Eng) Decleve, A. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Lieberman, M.; Boniver, J.; Kaplan, H. S. *Cancer Res* 39(11): 4322-4329; 1979.

One of the three nontumorigenic fibrotropic C-type viral isolates from C57BL/Ka mice, the BL/Ka(B) virus (which is the only one of the three capable of infecting normal hematopoietic and lymphoid cell populations of C57BL/Ka mice in vivo), was studied. Inoculation of this virus alone into neonates resulted in transient replication in the bone marrow, spleen, and occasionally the thymus. Thymocytes could, however, be permanently infected in such animals if BL/Ka(B) virus was coinoculated with the xenotropic BL/Ka(X) virus. Neonatal injection of BL/Ka(B) prior to fractionated whole-body irradiation yielded an increase in the percentage of virus-productive radiogenic lymphomas but a decrease in the incidence of this tumor. Injection of BL/Ka(B) into normal adult C57BL/Ka mice did not yield overt expression of virus replication in any tissues tested; latent infection could, however, be detected in the marrow and in the reticuloepithelium of the thymus. Whole-body x-irradiation of adults with 400 rads partially restored neonatal susceptibility of bone marrow cells to infection. BL/Ka(B) injection after fractionated whole-body irradiation of weanling C57BL/Ka mice increased the percentage of virus-positive lymphomas; in addition, a bone marrow cell subpopulation permissive for infection by the virus increased greatly soon after irradiation. (29 refs)

- 79-7057 A New Endogenous Primate Type C Virus Isolated from the Old World Monkey *Colobus polykomos*. (Eng) Sherwin, S. A. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD); Todaro, G. J. *Proc Natl Acad Sci USA* 76(10): 5041-5045; 1979.

A new, genetically transmitted retrovirus (CPC-1) was isolated from the Old World monkey *Colobus polykomos* and was readily transmitted to both feline and human cells in culture. Nucleic acid

hybridization studies revealed 50-70 copies of the CPC-1 genome in *C. polykomos* cellular DNA. Since related virologic sequences were detected in the DNA of all other Old World monkeys, as well as in the DNA of at least one ape species, the chimpanzee, this virus appears to have been genetically transmitted in primates for 30-40 million yr. CPC-1 showed a partial relationship to the type C virus previously isolated from stump-tail monkeys (MAC-1), as indicated by nucleic acid sequence homology, antigenic cross-reactivity of the major viral structural proteins, and similar host range in vitro. It was concluded that CPC-1 and MAC-1 belong to the same class of genetically transmitted primate type C viruses and as such represent the first example in primates of analogous endogenous retroviruses isolated from two distantly related species. (26 refs)

- 79-7058 Analysis of the Properties of a New Antigen Associated with Oncornavirus D. (Rus) Kosiakova, N. P. (D. I. Ivanovskii Inst. Virology, Moscow, USSR); Posevaia, T. A.; Zhdanov, V. M. *Vopr Virusol* (4): 381-385; 1979.

Properties of a new antigen associated with oncornavirus D were evaluated. HEp-2 cells or L 929 murine fibroblasts were infected with oncornavirus D and then incubated with the labeled precursors. The soluble antigens were obtained by solubilization with detergents; the presence of soluble antigen in the supernatant was assessed by the complement fixation reaction (CFR) with specific rabbit antiserum. The final precipitate was analyzed by polyacrylamide gel electrophoresis. Both HEp-2 and L 929 cells contained the peak of radioactivity corresponding to a protein with a mol wt of 98,000-100,000 daltons. (13 refs)

- 79-7059 Unusual Features of the Oncogenicity of Chicken Embryo Lethal Orphan (CELO) Virus in Hamsters. (Eng) Asch, B. B. (Dept. Pathology, Beth Israel Hosp., Boston, MA 02215); McCormick, K. J.; Trentin, J. J. *Prog Exp Tumor Res* 23: 56-88; 1979.

Previous studies concerning the in vitro and in vivo malignant transformation of hamster cells by chicken embryo lethal orphan (CELO) virus are reviewed, and the results of recently conducted studies are presented. No single characteristic morphologic pattern of CELO virus-transformed tumor cells was identified in the present studies; the morphology of such cells appeared to depend to some extent on the source of the cell. Alternatively, CELO virus may interact differently with the same type of target cell, thereby giving rise to distinctive morphology. Successful quantitative transformation procedures were dependent on conditions that restricted growth of normal cells. Expression of CELO virus-specific T-antigen varied in both the tumor and transformed cells induced by CELO virus, and it is likely that the synthesis of this antigen may in some cases be repressed in a tumor cell and then resumed at a later time under suitable conditions. It appears that the CELO virus T-antigen is not necessary for the maintenance of transformation induced in vivo or in vitro. There may be separate genes for CELO virus T-antigen and tumor-specific transplantation antigen in that the lack of the former did not affect the expression of the latter in CILT/2 cells. All of five cell lines established from CELO virus-induced tumors contained at least one type of virus-like particle (VLP), and two of four lines derived from cells transformed in 2% fetal calf serum had VLP detectable by electron microscopy. There is no evidence that indigenous VLP of the hamster are more than passengers in CELO virus-induced tumors. (68 refs)

- 79-7060 Avian Acute Leukemia Virus MC29: Conserved and Variable RNA Sequences and Recombination with Helper Virus. (Eng) Duesberg, P. H. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Bister, K.; Moscovici, C. *Virology* 99(1): 121-134; 1979.

The RNAs and proteins of five laboratory strains of defective avian acute leukemia virus MC29 were investigated for genetic variations. The RNAs shared 20 conserved T₁-oligonucleotides (ON) and differed in specific sets selected from 10 variable ON. Since some, but not all, variable and some conserved MC29-ON were shared with helper viruses, and since the 5' cap-ON of MC29 RNA rescued from the same nonproducer cell varied with that of the helper virus RNA, it was concluded that genetic variations in MC29 include recombination with helper virus. Oligonucleotide maps of the five MC29 RNAs showed eight variable ON in their 3' group-specific sections, only conserved ON in their internal-specific section, and mostly conserved ON in their 5' group-specific section (with the exception of variable 5' cap-ON and a lack of internal ON in one strain). The 110K proteins of the five strains were electrophoretically indistinguishable. The ratio of MC29 RNA to helper virus RNA in virions reflected, by a constant, the ratio of 110K MC29 to helper viral proteins in transformed cells. MC29 RNA appears to consist of two genetic units: one made of highly conserved 5' and internal-specific RNA sections, which codes for the 110K protein and appears to serve a primary function in oncogenicity; and the other made of the variable 3' group-specific RNA sections, which may affect oncogenicity indirectly. (36 refs)

- 79-7061 Role of Envelope Proteins of Paramyxoviruses in the Modification of Cell Membrane Antigens. (Eng) Eaton, M. D. (Dept. Medical Microbiology, Stanford Univ., Stanford, CA 94305). *Arch Virol* 61(4): 327-336; 1979.

The role of envelope proteins of paramyxoviruses in the modification of cell membrane antigens was studied. Modified Newcastle disease virus, and Sendai virus or virus fractions were used to immunize C3H/Bi/G mice. The effect of viral preparations with reduced F (fusion) protein activity was compared with that of equivalent amounts of active or inactive virus as measured by hemagglutination. Viral preparations without hemolytic activity showed diminished adsorption to tumor cell (ascites lymphoma induced by the Gross murine leukemia virus) membranes, and the immune response to these membranes in syngeneic hosts was diminished. An immunogenic material associated with paramyxovirus antigens was extracted from membranes with Triton X100 and desoxycholate. The results indicate that the F protein is a major factor in permanent adsorption and in causing cell membrane antigens to become immunogenic in syngeneic hosts. (21 refs)

- 79-7062 Histological and Cytological Evidence of a Condylomatous Lesion in Association with an Invasive Carcinoma of Uterine Cervix. (Eng) Syrjanen, K. J. (Dept. Pathology, Pajjat-Hame Central Hosp., Lathi, Finland). *Arch Geschwulstforsch* 49(5): 436-443; 1979.

A 38-yr-old woman underwent colposcopic examination after routine cytological smears showed cells suggesting epithelial dysplasia. Wartlike punctate areas and mosaic patterns were present in the cervical epithelium. Biopsy was indicative of carcinoma in situ, and conization was performed. The conization specimen yielded the diagnosis of invasive squamous cell carcinoma. Examination of the smears confirmed the presence of small dyskaryotic superficial keratinized cells derived from the superficial keratotic layers of condylomatous epithelium. Condylomatous intermediate cells and superficial cells with perinuclear halos were also present. In the colposcopy specimens, epithelial lesions typical of flat-type condyloma were found close to and mixed with the dysplastic areas. In the conization specimens, condylomatous lesions were closely associated with the invasive carcinoma. The patient underwent a Wertheim operation combined with radiotherapy, and was disease-free 16 mo later. Follow-up for any woman with condyloma cells in cervical smears is strongly recommended. (24 refs)

- 79-7063 Hepatitis B Virus Antigens in Human Primary Hepatocellular Carcinoma Tissues. (Eng) Goudeau, A. (Facultes de Medecine et de Pharmacie, Institut de Virologie, 2 bis, Boulevard Tonnelles, 37000 Tours, France); Maupas, P.; Coursaget, P.; Drucker, J.; Chiron, J. P.; Denis, F.; Diop Mar, I. *Int J Cancer* 24(4): 421-429; 1979.

The presence of hepatitis B virus (HBV) antigens was examined in specimens of liver tissue obtained at necropsy from black Senegalese patients suffering from primary hepatocellular carcinoma (PHC). The results were correlated with markers of hepatitis B infection in serum. Examination of 15 liver extracts for hepatitis B surface antigen (HBsAg) and core antigen (HBcAg) revealed HBsAg in 10/12 cases with HBsAg-positive serum and HBcAg in 3 cases. The HBsAg was detected in seven of eight livers by immunofluorescence and orcein staining. HBsAg-positive cells were located mainly in the peri-tumoral cirrhotic tissue, although positive hepatocytes were also found in tumor nodules in liver from one of the patients. HBcAg was found in five of seven cases by immunofluorescence in hepatocytes of the cirrhotic areas. HBcAg fluorescence was primarily nuclear but, in some lobules, a patchy cytoplasmic fluorescence was observed, suggesting a cytoplasm-nucleus pathway in the synthesis of the HBV core antigen. Electron microscopy was performed on two HBsAg- and HBcAg-positive cases. Fibrillar and crystalline cytoplasmic inclusions were observed in tumor cells. In the same cells, 20-25 nanometer virus-like particles were present in swollen cisternae of the endoplasmic reticulum. (34 refs)

See also:

- *(Rev.): 79-6605, 79-6623, 79-6633, 79-6634, 79-6635, 79-6641.
*(Chem.): 79-6801, 79-6841.
*(Phys.): 79-6893, 79-6903, 79-6904.
*(Immun.): 79-7064, 79-7068, 78-7070, 78-7071, 79-7072, 79-7080, 79-7082, 79-7095, 79-7097.
*(Epid.-Biom.): 79-7141, 79-7163, 79-7169.

IMMUNOLOGY

- 79-7064 Rejection of Adenovirus 2-transformed Cell Tumors and Immune Responsiveness in Syrian Hamsters. (Eng) Cook, J. L. (Natl. Inst. Allergy and Infectious Diseases, NIH, NCI, Bethesda, MD 20205); Kirkpatrick, C. H.; Rabson, A. S.; Lewis, A. M. *Cancer Res* 39(12): 4949-4955; 1979.

When newborn hamster tumor lines induced by adenovirus type 2-transformed cells were transplanted to older hamsters (sucklings 4-21 days old, weanlings after 21 days), the cell-mediated host defenses responsible for tumor graft rejection matured early in the second wk of life. Light microscopic examinations performed during the course of tumor development showed that the primary histopathological difference between progressing tumors removed from newborn or thymectomized weanling hamsters and regressing lesions from normal weanlings was the lack of an early, mononuclear cell infiltrate in neoplasms from newborn and thymectomized hosts. These results suggest that the maturation of cellular immunity determines resistance to tumor transplantation in this system. This conclusion was supported by the in vitro detection of concanavalin A-responsive lymphocytes in spleens from tumor-resistant suckling but not tumor-susceptible neonatal hamsters. Although the incomplete seeding of thymus-dependent lymphocytes to the peripheral lymphoid tissues of newborn hamsters may partially explain the deficient concanavalin A responses of neonatal spleen cells, there appears to be an additional requirement for a radioresistant, adherent accessory cell population. These findings suggest that the development of a cell-mediated immune response is necessary for the rejection of adenovirus type 2-transformed cells and transformed cell-induced tumors and that this response requires the interaction of T-cells and accessory cell populations. (21 refs)

- 79-7065 Suppression of the Immune Response in Tumor-bearing Mice. II. Characterization of Adherent Suppressor Cells. (Eng) Bluestone, J. A. (Lab. Herpes Virus Infection, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Lopez, C. *J Natl Cancer Inst* 63(5): 1221-1227; 1979.

The results of experiments in which adherent spleen cells from late (≥ 18 days postinoculation) tumor-bearing BALB/c mice suppressed lymphoproliferative and effector immunity, as evaluated by the mixed leukocyte culture and cell-mediated lympholysis assays, are reported. Procedures that eliminated T-cells or B-cells while enriching for macrophage populations significantly augmented the suppression, whereas removal of phagocytic and adherent cells abrogated the suppressive effect. It is concluded that the cells responsible for the suppression of cell-mediated immune responses in late tumor-bearing mice were of the monocyte-macrophage series. Furthermore, the suppressive influence was not due merely to the increased number of macrophages in tumor-bearing animals. The experiments clearly showed that the splenic macrophages, even at low concentrations, demonstrated a suppressive function. (33 refs)

- T. (Dept. Immunology, Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Seiryomachi 4-1, Sendai 980, Japan); Tachibana, T. *Gann Monogr Cancer Res* 23: 247-254; 1979.

Immune responses induced by inoculation of hybrid cells into normal and tumor-bearing C3H mice were studied. Primary tumor cells induced in a C3H mouse by 3-methylcholanthrene were fused with 8-azaguanine-resistant L cells, yielding two hybrid clones: hybrids of two tumor cells with one L cell; and hybrids of one tumor cell with one L cell. Both hybrid types expressed H-2k antigen, the tumor cell antigen, and L-cell antigen, and failed to produce tumors in a normal C3H mouse following ip or sc injection of 10^6 cells. Normal mice inoculated with hybrid cells were resistant to subsequent challenge with the parental tumor cells, the growth of tumor cells being suppressed by splenic lymphoid cells from the resistant mice. Suppression of tumor growth was also observed with immune splenic lymphoid cells passed through a nylon fiber column, but not with immune splenic cells treated with anti-Thy-1.2 serum and complement. When hybrid cells were injected into parental tumor-bearing mice, tumor growth was enhanced and cytotoxic T cells were generated. Elevated levels of antibody to the tumor cells and antigen-antibody complex were detected in the sera from these mice compared with sera from untreated tumor-bearing mice. The sera of the hybrid-cell-treated tumor bearers blocked at the level of the target cells and also inhibited the reactivity of immune spleen cells in vitro. It is concluded that the injection of viable hybrid cells can preferentially stimulate cellular immunity in normal mice while accelerating the humoral response in tumor-bearing mice, resulting in enhanced tumor growth. (19 refs)

- 79-7067 Expression of the Transformed Phenotype and Tumorigenicity in Somatic Cell Hybrids. (Eng) Marshall, C. J. (Dept. Molecular Genetics, Sidney Farber Cancer Inst., Boston, MA 02115). *J Cell Sci* 39: 319-327; 1979.

Two TA3B x REF and four BI x TA3B hybrids that show suppression of the transformed phenotype were tested for tumorigenicity in nude mice. Aliquots of cell suspensions (10^6 , 10^5 , and 10^3 cells) were injected sc into the rear flank of male nu/nu nude mice, 6-12 wk old. No tumors were produced from either of the two TA3B x REF hybrids, each of which contained one genome from each tumor producing parental strain, suggesting that both tumorigenicity and the transformed phenotype are very stably suppressed. BI x TA3B hybrids produced tumors in nude mice; these tumors arose after long latent periods (40-70 days), suggesting the selective outgrowth of a subset of variant hybrids. Selection in culture for anchorage-independent growth selected for tumorigenicity. Tumorigenic variants always exhibited an altered cytoskeleton. Variants selected in culture for the expression of the transformed phenotype did not show suppression of tumorigenicity, and variants selected for tumorigenicity expressed some (but not necessarily all) characteristics of the transformed phenotype, suggesting that the selected variant is not the only type that can be derived from a suppressed hybrid. (16 refs)

- 79-7066 Immune Responses Induced by Inoculation of Hybrid Cells in Normal and Tumor-bearing Mice. (Eng) Dei,

- 79-7068 Depression of Vaccinal Immunity to Marek's Disease by Infection with Reticuloendotheliosis Virus. (Eng)

Witter, R. L. (Regional Poultry Res. Lab., Science and Education Admin., Agricultural Res., US Dept. Agriculture, East Lansing, MI 48823); Lee, L. F.; Bacon, L. D.; Smith, E. J. *Infect Immun* 26(1): 90-98; 1979.

The effect of infection with low-virulence, tissue culture-propagated strains of reticuloendotheliosis virus (REV) on protective vaccinal immunity against Marek's disease (MD) lymphomas was investigated. Vaccinated chickens inoculated at hatching with $>10^4$ focus-forming units of REV and challenged with MD virus were poorly protected against MD lesion development; protective indices were 53-79% for strain CS ($p < 0.05$) and 42-49% for strain T ($p < 0.01$) compared to 78-100% for REV-free controls. Furthermore, the response of blood lymphocytes to mitogen stimulation and the antibody response to sheep erythrocytes and *Brucella abortus* were less in REV-inoculated chickens than in controls. The REV-induced depression of immune responses was more severe in chickens infected with mildly pathogenic strain T than in chickens infected with the apathogenic strain CS and was generally transient with both virus strains. Little or no depression of immune responses was observed in chickens inoculated with $<10^3$ focus-forming units of REV. These studies extend knowledge on the immunodepressive ability of low-virulence REV strains, establish that infection with these viruses depresses certain parameters of MD vaccinal immunity, and provide an important model for cellular immunity against virus-induced neoplasia in the chicken. (52 refs)

79-7069 Effect of Different Components of the Thymic Stroma on the Onset of AKR Leukaemia. (Eng) Fournier, M. (Immunology Res. Center, Institut Armand-Frappier, 531 des Prairies Blvd., P. O. Box 100, Laval-des-Rapides, Laval, Quebec, Canada); Potworowski, E. F. *Clin Exp Immunol* 37(3): 512-516; 1979.

Female AKR mice received weekly ip injections of one organ equivalent dose of insoluble thymic fraction (ITF) or soluble thymic fraction (STF) starting at 60 days of age and ceasing at the onset of leukemia. Three control groups [uninjected, injected with soluble spleen factor (SSF), and injected with insoluble spleen factor (ISF)] were established, with the latter two groups injected according to the same protocol used for the STF and ITF. The survival curves of the three control groups were similar, with death by leukemia beginning at day 225 and the 50% survival point reached at day 300. In the group injected with ITF, mice began to die at day 160; and the 50% survival point was reached at day 250. In the group injected with STF, mortality began at the same time as in the control groups; but the curve fell much more slowly. At the end of the experiment on day 350, 66% of the mice were still alive compared to 35% in the control groups. Preleukemic mice of 2, 4, 5, and 6 mo of age were sacrificed and their thymuses examined by immunofluorescence with anti-ITF and anti-STF sera. Strong positive fluorescence was obtained with anti-ITF in preleukemic and leukemic mice. Anti-STF staining was strong during the preleukemic period but could not be detected in the thymuses of leukemic mice. The acceleration of leukemia by ITF injections is in accordance with the hypothesis that an accumulation of thymocyte precursors is associated with the triggering of the disease. In the STF-injected group, the injected STF probably prevented the accumulation of lymphoblastoid cells. The results suggest disturbances in equilibrium between tumor-enhancing and fully differentiated immunocompetent T cells. (21 refs)

79-7070 Suppression of T Cell-mediated Immunity by Tumor Cells: Immunogenicity Versus Immunosuppression

and Preliminary Characterization of the Suppressive Factors. (Eng) Ting, C. C. (Lab. Cell Biology, NCI, Bethesda, MD 20014); Rodrigues, D.; Ting, R. C.; Wivel, N.; Collins, M. J. *Int J Cancer* 24(5): 644-655; 1979.

The effect of tumor cells (the Friend virus-induced FBL-3 and HFL/d leukemias and the chemically-induced EL-4 tumor and Meth A sarcoma) on the induction of cytotoxic T lymphocytes (CTLs) to alloantigens was studied using female C57BL/6 and BALB/c mice. The tumor cells were poorly immunogenic and were immunosuppressive as shown by their ability to suppress standard mixed lymphocyte culture reactions. This suppression acted mainly at the induction phase of the cytotoxic response and was not able to interfere with the killing activity of fully generated CTLs. In the FBL-3 system, at least two major components contributed to immunosuppression, one of viral and the other of nonviral origin. The viral component was sensitive to UV irradiation and could be pelleted after ultracentrifugation at 100,000 g. The non-viral component was UV-resistant and was retained in the supernatant fraction after ultracentrifugation. Friend virus and 12 commonly found murine viruses were excluded as possible causes for the immunosuppression; the immunosuppressive viruses are probably of endogenous origin and are defective in replication. The findings indicate that all tumor cells probably possess the immunosuppressive factor(s), which may account for their apparent lack of immunogenicity and the lack of proper immune response in the tumor-bearing hosts. (37 refs)

79-7071 Antigenic Expression in Somatic Hybrids and the Use of Cell Fusion in Tumor Xenogenization. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm 60, Sweden). *Gann Monogr Cancer Res* 23: 225-238; 1979.

Evidence for antigenic expression in somatic cell hybrids is discussed. Genetically determined antigens show a codominant (autonomous) expression, with the exception of hybrids produced by fusing the H-2-negative Ehrlich ascites tumor cells with other cells. In the latter case, the antigenic expression of the partner is suppressed but can reappear after chromosome losses. Fusion of β_2 -microglobulin- and HLA-negative Daudi cells with microglobulin-positive mouse or human cells leads to a reexpression of the missing HLA, and fusion of the TA3/Hauschka ascites tumor (low H-2 antigen expression) with normal fibroblast partners with different H-2 specificity leads to full reexpression of H-2a. Antigens and other markers related to differentiation are usually suppressed when expressor cells of a given lineage are fused with nonexpressor cells of a different lineage. In contrast, when expressor and nonexpressor cells of the same lineage are fused, codominant expression appears to be the rule. Virally determined and tumor-associated antigens show a wide range of behaviors. (45 refs)

79-7072 Humoral Reactions of BALB/c Mice during Tumor Induction by Moloney Sarcoma Virus. (Rus) Yakimenko, L. V. (Dept. Immunology Carcinogenesis, Inst. Problem Oncology, Kiev, USSR); Vetrova, E. P.; Kaminskaia, L. P.; Berdova, A. G.; Umanskii, Iu. A. *Vopr Onkol* 25(9): 46-50; 1979.

A study was designed to evaluate the humoral response in mice during tumor development induced by Moloney sarcoma virus (MSV). BALB/c mice were inoculated im with MSV. Antibody levels in the whole serum and its fractions as well as the number of antibody-forming cells (AFC) in the spleen were determined within

different time periods of inoculation. It was found that tumorigenesis did not affect the cytotoxicity of whole serum. The cytotoxic activity of the IgM-fraction increased in the middle of tumorigenesis, then decreased at the terminal stage, while cytotoxic activity of the IgG-fraction showed a progressive increase throughout the entire process of tumorigenesis. The number of AFC showed marked decrease (approx fourfold) during the period of max tumor development, while tumor regression was associated with an increase in the number of cells producing both 7S- and 19S-antibodies. (11 refs)

- 79-7073 Regulation of Granulopoiesis In Vitro. (Eng) Moore, M. A. (Dept. Developmental Hematopoiesis, Sloan-Kettering Inst. Cancer Res., New York, NY 10021). In: *Hematopoietic Cell Differentiation. Proceedings of the ICN-UCLA 1978 Symposium on Molecular and Cellular Biology held in Keystone, CO, 10 March 1978*. Golde, D. W.; Cline, M. J.; Metcalf, D.; Fox, C. F., eds. (New York: Academic Press) Vol. 10, 504 pp.; 445-459; 1978.

Studies concerning the regulation of granulopoiesis in vitro are reviewed. Mature granulocytes and their products indirectly inhibit granulocyte-macrophage progenitor cells (CFU-c) in vitro by decreasing the production and release of colony-stimulating factors (CSF) by monocytes and macrophages. Granulocyte colony-inhibiting activity (CLA) has no inhibitory effect on colony formation stimulated by an exogenous source of CSF and does not act directly on CFU-c or on the CSF molecule. Studies of CIA in the granulocytes of patients with chronic myeloid leukemia suggest that the production and response to CIA are quantitatively, not qualitatively, defective in this disease. The capacity of serum to stimulate granulocytic colony formation in vitro involves at least three types of activities: CSF, potentiating factors that enhance CSF action, and inhibitory factors with various degrees of specificity. Macrophages elaborate prostaglandin E (PGE) in response to macrophage-activating agents. The extent of prostaglandin synthesis is determined by the concentration of CSF to which the cells are exposed, which suggests that PGE may play a physiological role in limiting the positive feedback of macrophage-derived CSF. Some retention of regulatory responsiveness was observed in myeloid leukemias, particularly a dependence on CSF for in vitro proliferation of leukemic cells from patients with acute and chronic myeloid leukemia. In vitro transformation of continuous bone marrow cultures with Friend virus produced phenotypic changes comparable to those seen with human myeloid leukemia. These in vitro studies demonstrate that a subtle regulatory imbalance may play a major role in clonal dominance of transformed pluripotential stem cells and committed granulopoietic progenitor cells. (24 refs)

- 79-7074 Fc Receptors on Myeloid Leukaemic Cells: Comparison Between Assays of Rosette-forming Cells. (Eng) Ridway, J. C. (Dept. Pathology, Victoria Hosp., Blackpool FY3 8NR, England); Taylor, G. M.; Harris, R. *J Immunol Methods* 29(3): 271-277; 1979.

The ability of sheep RBC sensitized with rabbit anti-sheep RBC antibody (SEA) and human anti-D-coated RBC (HEA) to identify Fc receptors on blood WBC from normal individuals and from patients with myeloid leukemia was compared using the rosette-forming cells (RFC) assay. Differences were found between the assays in both groups, indicating the heterogeneity of Fc receptors with respect to affinity for marker and for Fc-bearing WBC. In

normal cells, WBC formed more rosettes with the SEA marker, while in several different myeloid leukemias, there were generally more HEA-RFC than SEA-RFC. This was particularly noticeable when the proportion of monocytoid cells in the blood was high. The variability of results seen between markers and within morphologically determined types in myeloid leukemia could be due to heterogeneity in expression of the receptor, and the Fc receptor density may be increased in active cells of a malignant disease. Although SEA are more efficient than HEA for the detection of Fc receptors on normal WBC and neutrophils, the usefulness of SEA in detecting myelomonocytic blasts is limited unless the blood is first depleted of lymphocytes and neutrophils. (8 refs)

- 79-7075 Rapid In Vivo Assay of Mouse Natural Killer Cell Activity. (Eng) Riccardi, C. (Inst. Pharmacology, Univ. Perugia, 06100 Perugia, Italy); Puccetti, P.; Santoni, A.; Herberman, R. B. *J Natl Cancer Inst* 63(4): 1041-1045; 1979.

Rapid elimination of tumor cells from some organs was detected in mice following the iv injection of tumor cells labeled in vitro with [¹²⁵I]5-iodo-2'-deoxyuridine. Recovery of radioactivity in different organs (spleen, liver, and lungs) was reduced in mice with high natural killer (NK) cell reactivity in their spleens, as measured in vitro by concomitant short-term ⁵¹Cr release assay. Considerable parallelism between in vitro and in vivo reactivities against two mouse lymphomas and a human myeloid cell line was found in mice of different strains and ages. Similarly, various immunopharmacologic treatments had comparable effects on in vitro and in vivo reactivities. These findings are consistent with the hypothesis that rapid cytolysis of tumor cells occurred in vivo and that NK cells played a major role in their elimination. (19 refs)

- 79-7076 Myasthenia Gravis and Lymphoma. A Clinical and Immunological Association. (Eng) Davis, S. (Dept. Neurology, Royal Melbourne Hosp., Melbourne, Australia); Schumacher, M. J. *JAMA* 242(19): 2096-2097; 1979.

Myasthenia gravis (MG) developed in a 62-yr-old man 6 mo after radiotherapy (three doses of 3,552 rads, 3,500 rads, and 4,000 rads, respectively) for poorly differentiated nodular lymphoma. T-cell immunodeficiency, including profound T-cell lymphopenia, impaired delayed hypersensitivity responses, and failure of a thymus-dependent antibody response to *Salmonella adelaide* flagellin, was demonstrated after MG was diagnosed. It is concluded that when MG and lymphoma coexist, both may have been triggered by an immunological defect. (9 refs)

- 79-7077 Immunity as the Predominant Factor Determining Metastasis by Murine Lymphomas. (Eng) Davey, G. C. (Div. Tumour Immunology, Chester Beatty Res. Inst., Belmont, Sutton, Surrey, England); Currie, G. A.; Alexander, P. *Br J Cancer* 40(4): 590-596; 1979.

The metastatic behavior of the L5178E (non-M) lymphoma and a highly metastatic subline L51787ES (M) was studied in syngeneic DBA2 mice. The non-M tumor rarely metastasized in intact syngeneic mice but produced extensive and rapidly lethal metastases when implanted into irradiated recipients. The metastatic behavior of the M subline was unaffected by irradiation of the host. By conventional transplantation criteria, the non-M tumor was more immunogenic than the M subline. Both tumors,

however, produced similar responses in a lymph node wt-gain assay. Host-cell infiltration of the tumors growing sc was much greater in the non-M than the M, the infiltrating cells being Fc-receptor-positive and maturing into macrophages after 2 days in vitro. It was concluded that while spontaneous in vitro motility of the M cells is much greater than that of the non-M, the metastatic behavior of the tumors is clearly determined by host immunologic responses. (11 refs)

- 79-7078 Hypothesis: Non-Hodgkin Lymphomas are Abnormal Immune Responses. (Eng) Habeshaw, J. A. (I.C.R.F. Gordon Hamilton Fairley Lab., St. Bartholomew's Hosp., West Smithfield, London EC1A 7BE, England). *Cancer Immunol Immunother* 7(1): 37-42; 1979.

Lymph-node biopsies from 174 patients with a confirmed diagnosis of non-Hodgkin lymphoma (NHL) were examined. Cell suspensions made from the affected nodes were studied for expression of surface antigens by immunofluorescence with specific antisera. Surface immunoglobulin expression and presence of surface receptors were also assessed. Tumors of undifferentiated cells (lymphoblastic lymphoma), of which there were 16 cases, showed the phenotypes of stem cells in 4 cases and of human thymus-leukemia-associated antigen (HTLA)-positive T cells in 7 cases. Five cases of B lymphoblastic lymphoma showed origin from B cells early in the maturation sequence at the time of either the primary or pre-primary immune response. Fifty-four patients had lymphocytic lymphoma, which was often associated with chronic lymphocytic leukemia. Most of these tumors appeared to arise from pre-primary immune response B lymphocytes. Tumors derived from follicular cells (centroblastic, centrocytic, or mixed tumors) were studied in 72 patients. These tumors showed a mix of B cell phenotypes, of T cells associated with a monoclonal B-cell component, and of cells with null-cell phenotypes. Immunoblastic and plasmablastic tumors, and lymphoplasmacytoid tumors, also showed a mix of these phenotypes. It is therefore concluded that most cases of NHL in humans are derived from primary or preprimary immune response B lymphocytes (as in lymphocytic lymphoma), germinal center B cells with a T-cell-predominant phase, or post-follicular memory or proplasma cells which may be blast-transformed (as in immunoblastic lymphoma) or quiescent (as in lymphoplasmacytoid lymphoma). Surface markers show that in the majority of tumors, the "neoplastic" B cell population was derived from a clone undergoing antigen-driven expansion in a follicular or post-follicular immune reaction. It is proposed that NHL represents an abnormal immune response in which the proliferating cells become frozen in an attitude of proliferation by failing to terminate the response in the normal way. (48 refs)

- 79-7079 Teratocarcinoma Transplantation Rejection Loci: An H-2-linked Tumor Rejection Locus. (Eng) Siegler, E. L. (Johns Hopkins Sch. Medicine, Baltimore, MD 21218); Tick, N.; Teresky, A. K.; Rosenstrauss, M.; Levine, A. J. *Immunogenetics* 9(3): 207-220; 1979.

Teratocarcinoma 129/Sv was 100% transplantable in syngeneic 129/Sv mice, but did not form tumors in BALB/c, C3H/He, or C57BL/6 mice, even though 129/Sv stem cells do not express detectable H-2 antigens. This tumor was 100% transplantable in F₁ hybrids of 129/Sv mice with the other three strains. Backcross and F₂ mice segregated the BALB/c, C3H/He, and C57BL/6 tumor transplantation rejection loci in a way suggesting that each strain has one or two such loci. The teratocarcinoma transplantation re-

jection locus in BALB/c and C3H/He mice seemed to be on chromosome 17, eight to nine recombination units from the H-2 complex. C57BL/6 mice apparently had the 129/Sv tumor-accepting (sensitive) allele at the H-2-linked locus but rejected the tumor because of antigenic differences at a second locus. These major teratocarcinoma transplantation rejection loci determined tumor acceptance or rejection after inoculation of high doses of tumor tissue (750 µg tumor protein). A number of minor genetic factors apparently affected the efficacy of tumor rejection and caused complete tumor rejection at lower tumor doses (7.5-75 µg tumor protein). (32 refs)

- 79-7080 Enhancement of Experimental Tumors in Mice by Treatment with Concanavalin A. (Eng) Ekstedt, R. D. (Dept. Microbiology, Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL 60611). *J Natl Cancer Inst* 63(4): 1065-1069; 1979.

To investigate the effect of lectins on tumor induction and development, weanling BALB/c mice received ip injections of 300 µg concanavalin A (Con A) prior to and at 48-hr intervals (3x/wk) after challenge with Moloney murine sarcoma virus (M-MuSV), 3-methylcholanthrene (MCA), or TEPC-15 plasmacytoma cells. These mice showed an enhancement of tumor induction or development. With the M-MuSV and MCA systems, this enhancement was evidenced by larger tumors and, in the MCA system, by more devastating tumors. M-MuSV-induced tumor regression was more prolonged in Con A-treated mice. In the TEPC-15 system, enhancement was evidenced by more rapid mortality in treated animals. (24 refs)

- 79-7081 Peritoneal Macrophages from Adjuvant Arthritic Rats Enhance Tumour Cell Growth In Vitro. (Eng) Binderup, L. (Dept. Pharmacology, Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark); Bramm, E.; Arrigoni-Martelli, E. *Experientia* 35(9): 1230-1232; 1979.

The effects of peritoneal macrophages from rats with adjuvant arthritis (AA, a chronic inflammatory disease triggered by immunologic mechanisms) on the in vitro growth of two rat tumor cell lines, Yoshida sarcoma (YS) and ascites hepatoma AH-13, were studied. AA was induced in female Lewis rats by injection of heat-killed *Mycobacterium butyricum*. Macrophages from arthritic rats, but not those from normal control rats, consistently enhanced [³H]thymidine (TdR) incorporation into YS cells, the greatest enhancement being seen with 10⁶ cells/ml taken on day 21 after the induction of AA. All tumor cell cultures contained >90% viable cells after the addition of macrophages. Nonadherent host cells did not appear to interfere with the macrophage/tumor cell assay. Thus, macrophages from rats with AA appear to have a decreased ability to deal with tumor cells. It is suggested that the immunologic commitment of the macrophages could interfere with their regulation of tumor cell proliferation in vivo. (15 refs)

- 79-7082 Tumor-enhancing Suppressor Activator T Cells in Spleens and Thymuses of Tumor Immune Mice. (Eng) Hellstrom, I. (Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, Washington 98104); Hellstrom, K. E.; Bernstien, I. D. *Proc Natl Acad Sci USA* 76(10): 5294-5298; 1979.

The role of suppressor T cells in tumor immunity was investigated by studying the effect of adoptively transferred syngeneic lymphoid cells on the growth of primary Moloney sarcoma virus (MSV)-induced sarcomas in BALB/c mice. Twenty-day-old BALB/c mice were inoculated with MSV and 1 or 6 days later were injected iv with cells from the thymus, spleen or lymph nodes of mice whose MSV-induced sarcomas had regressed 2-3 mo earlier. Thymus cells from normal BALB/c mice did not change the incidence of regression of primary MSV-induced sarcomas. Thymus and spleen cells from MSV regressors significantly decreased the extent to which primary MSV sarcomas regressed. A small tumor-enhancing effect was observed with the lymph node cells. The cells responsible for this tumor-enhancing effect carried the Thy 1 marker. They were not demonstrable in the thymuses of normal untreated mice or in mice immunized against or bearing methylcholanthrene (MCA)-induced sarcomas. The tumor-enhancing cells were not destroyed by administration of 400 rads of whole body radiation. The effect of the irradiated cells, however, was seen only in the presence of a normal nonirradiated T-cell population. Similar results were obtained with a transplantable MCA-induced, murine leukemia virus antigen-negative sarcoma, MCA-1460. These results support the concept that relatively radioresistant thymus cells from immune mice can enhance tumor outgrowth by interacting with radiosensitive T cells that are present in nonimmune mice. (15 refs)

- 79-7083 Studies on Metastases. I. Role of Sensitization and Immunosuppression. (Eng) Seshadri, M. (Medical Div. (RBOH), Bio-Medical Group, Bhabha Atomic Res. Center, Trombay, Bombay 400 085, India); Poduval, T. B.; Sundaram, K. *J Natl Cancer Inst* 63(5): 1205-1210; 1979.

Factors involved in the observed metastasis of normally nonmetastatic fibrosarcoma to the regional axillary lymph nodes following severe immunosuppression of inbred Swiss mice were investigated. The extent of metastasis was dependent on the severity of lymphocyte depletion and the initial number of tumor cells injected. Sensitization of the host to the tumor was important in prevention of metastasis: Metastasis was induced only if the immunosuppressive treatment occurred within 3 days of tumor inoculation. Antitumor immunity was adoptively transferred by the splenocytes from animals given immunosuppressive treatment with x-rays or hydrocortisone acetate on day 14. Though spleen cells from animals given both immunosuppressants did not have this property, the fact that no metastasis was observed even in doubly immunosuppressed mice indicated sensitization to tumor cells. Lymphocyte number was also important: Injection of splenocytes from normal animals to tumor-bearing mice significantly reduced the occurrence of metastases. (23 refs)

- 79-7084 Immunologic Abnormalities in Melanoma-prone Families. (Eng) Dean, J. H. (Immunobiology Section, Environmental Biology Branch, Natl. Inst. Environmental Health Science, Box 12233, Research Triangle Park, NC 27709); Greene, M. H.; Reimer, R. R.; LeSane, F. V.; McKeen, E. A.; Mulvihill, J. J.; Blattner, W. A.; Herberman, R. B.; Fraumeni, J. F. *J Natl Cancer Inst* 63(5): 1139-1145; 1979.

Extensive immunologic studies were carried out in 60 members of four families prone to cutaneous malignant melanoma (CMM) and a genetically determined precursor nevus syndrome. The most consistent finding was a diminished in vitro response to pooled alloantigens in one-way mixed leukocyte culture (MLC) and a tendency

toward low T-lymphocyte and B-lymphocyte levels. When compared with controls, low B-lymphocyte levels and reduced MLC responses were found not only in family members with CMM and/or precursor nevi but also in unaffected blood relatives and spouses. The genesis of the immune dysfunction and its possible relationship with melanoma pathogenesis remain to be clarified. (34 refs)

- 79-7085 Circulating Immune Complexes as Possible Cause for Anticomplementary Activity in Humans with Malignant Melanoma. (Eng) Gupta, R. K. (Div. Oncology, CHS 54-140, UCLA Sch. Medicine, Univ. California, Los Angeles, CA 90024); Theofilopoulos, A. N.; Dixon, F. J.; Morton, D. L. *Cancer Immunol Immunother* 6(4): 211-221; 1979.

Sera from 98 melanoma patients, 20 noncancer patients with immune complex-associated disease, and 90 normal donors were analyzed for anti-complementary (AC) activity by the complement consumption method. Some of these sera were also tested for immune complex-like materials by the Raji cell radioimmune assay. In addition, serum samples from 10 melanoma patients were analyzed serially to correlate the AC activity with clinical course. Significant levels of AC activity were found in 45% of melanoma sera, 75% of nonmalignant immune complex-associated disease sera, and 10% of normal donors' sera. In some patients, AC activity decreased until no longer detectable as their disease progressed. AC-negative serum samples taken from melanoma patients late in the course of disease when the tumor burden was large became AC-positive when mixed with autologous or allogeneic serum samples taken earlier at the time of little or no tumor burden. The early serum samples contained antibodies against autologous tumor extracts, as shown by a complement fixation test. Absorption of early serum samples with cultured allogeneic melanoma cells reduced their ability to consume complement when mixed with autologous late serum samples, suggesting the presence of free antigen in the latter. The mixed samples of early and late sera and the sera positive in the complement consumption test contained heavy nonmonomeric IgG. Therefore, the AC activity of melanoma sera could be due to tumor-associated antigen-antibody complexes. (49 refs)

- 79-7086 Immune Response to Melanoma Extracts in Three Melanoma-Prone Families. (Eng) Vandenbark, A. A. (Surgical Res. Lab., Veterans Admin. Medical Center, 3710 SW U.S. Veterans Hosp. Rd., Portland, OR 97207); Greene, M. H.; Burger, D. R.; Vetto, R. M.; Reimer, R. R. *J Natl Cancer Inst* 63(5): 1147-1151; 1979.

Immune reactivity to melanoma extracts was measured by the leukocyte adherence inhibition (LAI) test in 40 members of three melanoma-prone families. The melanoma patients had a wide range of responsiveness to the extract, the highest responder being a 10-yr survivor. As a group, family members (including spouses) without disease had significantly elevated LAI responses compared with those of unrelated controls ($p < 0.01$). Within the families, members with close exposure to melanoma patients for ≥ 10 yr had a significantly higher response to melanoma antigen than did members with 0-5 yr of close exposure ($p < 0.05$). Responses of spouses and members at high risk of developing melanoma (B-K mole syndrome) also correlated with length of exposure to patients, which suggests that the elevated LAI response was not genetically determined. The high frequency of positive responses to melanoma antigens in these families, particularly in spouses,

suggests the presence of transmissible melanoma-associated material capable of immunizing persons in contact with melanoma patients. (34 refs)

- 79-7087 In Vitro Lymphocyte Reactivity to Soluble Tumor Extracts in Sinclair Melanoma Swine. (Eng) Aultman, M. D. (Sinclair Comparative Medicine Res. Farm, R.D. 3, Columbia, MO 65201); Hook, R. R. *Int J Cancer* 24(5): 673-678; 1979.

An antigen-stimulated active rosette assay was adapted as an in vitro assay for the detection of lymphocyte reactivity to soluble tumor extracts. An increase in active rosette-forming cells (A-RFC) occurred only when sensitized lymphocytes from Sinclair melanoma swine were stimulated with specific sensitizing antigen. Lymphocytes from melanoma swine reacted in vitro to 3 M KCl extracts of autologous and allogeneic melanomas but did not react to 3 M KCl extracts of autologous and allogeneic swine skin. Lymphocyte reactivity to allogeneic melanoma extract (AME) was demonstrated by 84.8% of the melanoma swine, as compared to 23.5% of normal swine. The reactivity of the melanoma swine lymphocytes to AME was not due to reactivity of the lymphocytes to normal skin antigens or fetal swine antigens present in the AME. Lymphocytes from three melanoma swine increased A-RFC after incubation with each of nine different AME; thus the ability to stimulate lymphocyte reactivity was not limited to a single AME. The data indicate that a tumor-related immune response occurs in melanoma swine and that in vitro lymphocyte reactivity is directed towards a tumor-associated antigen or antigen-like substance present in 3 M KCl extracts of swine melanoma. (10 refs)

- 79-7088 Solid Tumors Complicating Hodgkin's Disease: A Report on Two Patients with Immunoglobulin Deficiency. (Eng) O'Sullivan, D. D. (Div. Oncology/Hematology, Chicago Medical Sch., Chicago, IL 60664); Raghuprasad, P.; Ezdinli, E. Z. *Arch Intern Med* 139(10): 1131-1134; 1979.

The development of multiple epithelial malignant neoplasms following radiotherapy and intensive chemotherapy for Hodgkin's disease is reported in two patients. At the time of diagnosis of the second primary tumor, both patients had been in prolonged complete remission, and serum immunoglobulin deficiencies were detected. In one case, there was no detectable serum IgA on several occasions prior to the discovery of adenocarcinoma of the lung and kidney. In the second case, no secretory IgA was detected in the saliva, and some degree of serum IgA, IgG, and IgM deficiency was present. The second patient had well-differentiated squamous cell carcinomas of the perineum, vagina, and cervix uteri, each of which was a separate primary neoplasm. A literature review indicated that the incidence of nonhematological cancers in patients with Hodgkin's disease varies from 1.5% to 6.6%. The authors concluded that there is a fivefold increase in the incidence of solid tumors in Hodgkin's disease patients compared with the general population. (19 refs)

- 79-7089 Suppressor Adherent Phagocytic Cells in Solid Tumors: A Postulated Escape Mechanism. (Eng) Parks, R. C. (AMC Cancer Res. Center and Hosp., 6401 West Colfax Ave., Lakewood, CO 80214). *Med Hypotheses* 5(9): 1017-1023; 1979.

A localized graft-vs-host (GVH) reaction was used to assess the cellular immunity of BALB/c mice bearing the progressively growing allogeneic melanoma S91-TMS. Splenic lymphocytes from these mice were inoculated into the hind footpads of (BALB/c x DBA/1)F₁ mice, and the GVH reaction was measured in the popliteal lymph nodes. The growing tumor evoked a hyperactive cell-mediated immune response, and an adherent phagocytic cell (APC) population isolated from the tumor effectively inhibited this specific immunologic activity. An important factor in the successful growth of the immunogenic tumor thus appears to be a coterminous population of APC that has the functional capacity to specifically nullify, in situ, cell-mediated immunity directed against the neoplasm. It is suggested that the APC population may originate in response to homeostatic factors associated with tissue damage and change, thus benefitting primary and possibly secondary inchoate tumor development via the inhibition of immunologic recognition and rejection responses that the host generates against the neoplasm. (35 refs)

- 79-7090 Beta-Glucuronidase Deficiency in Neutrophils of Patients with Precancerous States of the Larynx. (Pol) Lisiewicz, J. (Klinika Laryngologii, Instytutu Chorob Układu Nerwowego i Narządów Zmysłowych, Śląskiej Akademii Medycznej, ul. Kopernika 17, 31-501 Krakow, Poland); Gierek, T.; Kusnierczyk, W.; Pilch, J. *Przegl Lek* 36(8): 609-611; 1979.

The β -glucuronidase (BG) and acid phosphatase (AP) activities of peripheral blood neutrophils were studied in 24 men with precancerous states of the larynx and in 20 healthy male controls by determining the enzyme-positive and enzyme-negative cell counts and the enzyme activity variations within the enzyme-positive cell population. No differences were found in the AP activities between the two groups. In contrast, the BG activity was significantly lower in the patients than in the controls. The most striking difference was the nearly complete absence of BG-positive neutrophils with high enzyme activity in the patients; the majority of their BG-positive cells showed only traces of enzyme activity. The BG deficiency is assumed to be due to the neutrophil-mediated cytotoxic effect against mammalian tumor cells. (12 refs)

- 79-7091 Human Lung Tumor-associated Antigens of 32,000 Daltons Molecular Weight. (Eng) Kempner, D. H. (Dept. Pediatric Hematology, Oncology, and Immunology, Cedars-Sinai Medical Center, Halper Bldg. Rm. 618, Los Angeles, CA 90048); Jay, M. R.; Stevens, R. H. *J Natl Cancer Inst* 63(5): 1121-1129; 1979.

Lung tumor-associated antigens of approx 32,000 daltons were recognized by the use of sensitive radioimmunoassays and rabbit antisera, one raised against an extract of pooled human malignant lung tissues and another raised against a cell line derived from a human squamous cell carcinoma of the lung. These antigens differed from antigens described previously, including carcinoembryonic antigen and α -fetoprotein. The antigens were detected on 13/13 lung tumors (of all histologic types), fetal tissue, normal brain, 2/8 colon tumors, 2/9 prostate tumors, and 2/3 breast tumors, as well as on cell lines derived from lung tumors, neuroblastoma, human amnion, colon adenocarcinoma, and bladder tumors. They were not detectable on normal lung, liver, kidney, colon, or prostate tissues or on cell lines derived from osteosarcoma, fetal lung fibroblasts, transitional cell carcinoma, and squamous cell carcinoma of the skin. Lung tumors of different histologic types were concluded to express common, tumor-

associated oncofetal antigens that are found less often in tumors of other organs. (44 refs)

- 79-7092 **Antigenic Expression on Mouse Hybrid Cells.** (Eng) Tachibana, T. (Dept. Immunology, Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Seiryomachi 4-1, Sendai 980, Japan); Dei, T. *Gann Monogr Cancer Res* 23: 239-245; 1979.

The eclipse phenomenon of H-2 antigenic expression was studied in somatic cell hybrids formed between L cells and non-Ehrlich tumor cells. Suppression of the H-2 antigenic expression (ie, the eclipse phenomenon) similar to that previously seen in hybrids between L and Ehrlich cells was observed in hybrids between L cells and FM3A ascitic mammary tumor cells and between L cells and spontaneous mammary carcinoma (SMCA) cells. FM3A cells expressed mouse mammary tumor-specific surface antigen (MM antigen), which was lacking in the SMCA cells from which they were derived by serial passage through a syngeneic host. Both hybrid populations showed expression of the MM antigen with simultaneous reduction of the H-2 antigen expression. It is suggested that the suppression of the surface antigens of the partner is produced by mammary tumor cells (Ehrlich, FM3A, and SMCA). (14 refs)

- 79-7093 **Abrogation of the Phenomenon of Leukocyte Adherence Inhibition by Excess Circulating Tumor Antigen.** (Eng) Thomson, D. M. (Div. Clinical Immunology and Allergy, Montreal General Hosp. Res. Inst., McGill Univ., Montreal H3G 1A4, Canada); Tataryn, D. N.; Schwartz, R.; MacFarlane, J. K. *Eur J Cancer* 15(9): 1095-1106; 1979.

The patterns of peripheral blood leukocyte (PBL) nonadherence to glass were compared in a group of control subjects, a group of patients with localized colon and breast cancer, and another group with metastatic colon and breast cancer. When incubated with extracts of unrelated cancer, PBL from patients with localized cancer showed nonadherence equal to those of controls. When these same leukocytes were incubated with extracts of the sensitizing cancer, leukocyte nonadherence was significantly higher than in control subjects. The leukocytes from patients with metastatic cancer exhibited a high leukocyte nonadherence, whether they were incubated with specific (sensitizing cancer) or nonspecific tumor extracts. The leukocyte adherence inhibition (LAI) reactivity was abrogated by preincubation with the sensitizing tumor-specific antigen (TSA) either from solid tumor or isolated from serum. The tumor antigen coat on the leukocytes from metastatic cancer patients was removed by trypsinization of the leukocyte surface, which restored its capacity to react with the sensitizing tumor antigen. It is concluded that the nonadherence of leukocytes from patients with localized or metastatic cancer is induced by the immunologically specific binding of TSA to the monocyte's cell surface. In leukocytes from patients with localized cancer, this reaction takes place in vitro, whereas in those from patients with metastatic cancer, TSA binding occurs in vivo. (27 refs)

- 79-7094 **α_1 -Fetoprotein mRNA of Rat Yolk Sac and Hepatoma.** (Eng) Chiu, J. F. (Dept. Biochemistry, Univ. Vermont, Coll. Medicine, Burlington, VT 05405); Dechamphai, W.; Commer, P. *Nucleic Acids Res* 7(1): 239-249; 1979.

Rat yolk sac α -Fetoprotein (AFP) messenger RNA (mRNA) was purified and characterized. AFP mRNA was isolated and purified to apparent homogeneity by means of immunoadsorption and oligo (dT) cellulose affinity chromatography. Purified AFP mRNA migrated as a 21S peak in 2.5% sodium dodecyl sulfate (SDS) polyacrylamide gels. The translation product of this mRNA in micrococcal nuclease-treated reticulocyte lysate was identified as AFP by specific immunoprecipitation, SDS-gel electrophoresis and tryptic digestion analysis. DNA complementary to AFP mRNA was synthesized with avian myeloblastosis virus RNA-dependent DNA polymerase. This AFP complementary DNA was used as a probe to quantitate AFP mRNA in the developing rat liver and to compare the complexity and diversity of AFP mRNA derived from the normal rat liver and Morris hepatoma 7777. The amount of functional AFP mRNA decreased during liver development. There was little, if any, AFP mRNA in the adult rat liver. A high degree of homology between the AFP mRNA sequences of yolk sac and hepatoma was also found. (31 refs)

- 79-7095 **Further Studies of a Macrophage Chemotaxis Inhibitor (MCI) Produced by Neoplasms: Murine Tumors Free of Lactic Dehydrogenase Virus Produce MCI.** (Eng) Snyderman, R. (Lab. Immune Effector Function, Howard Hughes Medical Inst., Duke Univ. Medical Center, Durham, NC 27710); Cianciolo, G. J. *J Reticuloendothel Soc* 26(4): 453-458; 1979.

The possibility that contamination with lactic dehydrogenase virus (LDV) causes the biologic activity of a macrophage chemotaxis inhibitor (MCI) found in several murine tumors was investigated in mouse hepatoma 129. Serum containing LDV or the cell-free supernatant (CFS) or ultrafiltrate (MCI) from long-term, ascites-passaged hepatoma cells substantially inhibited macrophage accumulation in the peritoneal cavities of phytohemagglutinin-treated C3Heb/Fej mice. CFS, not MCI, contained infectious LDV. CFS prepared from two different solid tumors and CFS and MCI prepared from hepatoma 129 ascites cells were also free of infectious LDV but inhibited in vivo macrophage accumulation by 63%-79%. Urine taken from mice 8 days after the ip injection of 5×10^6 hepatoma ascites cells inhibited macrophage accumulation by 76%, whereas urine from age-matched controls yielded only 18% inhibition. The urine was free from infectious LDV. The release of MCI by neoplasms may protect developing tumors from immunologic destruction during early phases of their growth. (13 refs)

- 79-7096 **Identification of a Tumor-specific Antigen in the Insoluble Fraction of Human Nephroblastoma.** (Preliminary Communication). (Eng) Okada, S. (Dept. Pathophysiology, Cancer Res. Inst., Kanazawa Univ., Kanazawa 920, Japan); Itaya, K.; Kurata, Y. *Eur J Cancer* 15(9): 1085-1093; 1979.

Physicochemical characteristics of a nephroblastoma-specific antigen were studied following its isolation. The insoluble fraction of three nephroblastomas was solubilized using desoxycholate. The soluble product obtained from this treatment was partially purified by gel filtration and used to produce sera by immunization of guinea pigs. After appropriate absorption, the antisera were reactive in gel diffusion only with nephroblastoma fractions and with sera from three patients with nephroblastoma. No reactivity was observed with fractions of normal adult or fetal organs, with a variety of other tumor types (including renal cell carcinoma, transitional cell carcinoma, stomach adenocarcinoma, colon

adenocarcinoma, epidermoid carcinoma of the cervix, hepatoma, lymphosarcoma, and rhabdomyosarcoma), or with control sera from 30 patients with nonmalignant diseases. The antisera also failed to react with carcinoembryonic antigen, with α_1 -fetoprotein, or with fetuin. The antigen also appeared to be different from the previously detected antigens in nephroblastoma, such as W-antigen and Wilms' tumor-associated antigen. Preliminary physicochemical studies indicated that this soluble product is nearly homogeneous and that the specific antigen has a mol wt of 60,000. The presence of the nephroblastoma-specific antigen in three nephroblastomas and in sera of three patients with this tumor suggests that it is a common antigen within nephroblastomas. (26 refs)

- 79-7097 Autoimmune and Lymphoproliferative Disease in (B6- G_{ix} x 129) F_1 Mice: Relation to Naturally Occurring Antibodies Against Murine Leukemia Virus-related Cell Surface Antigens. (Eng) Obata, Y. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Tanaka, T.; Stockert, E.; Good, R. A. *Proc Natl Acad Sci USA* 76(10): 5289-5293; 1979.

The characteristics and incidences of diseases in G_{ix} * F_1 hybrid C57BL/6 mice were compared with those in G_{ix} * F_1 mice and with those in the two parental strains, B6- G_{ix} * and 129. Only the G_{ix} * F_1 mice produce natural antibodies to G_{ix} antigen, the type-specific determinant of the major envelope glycoprotein of murine leukemia virus (MuLV). After 14 mo of age G_{ix} * F_1 mice developed a pronounced diffuse glomerulonephritis similar to that seen in systemic lupus erythematosus in man. These lesions occurred in 29/77 G_{ix} * F_1 mice but not in G_{ix} * F_1 , B6- G_{ix} *, or 129 mice. Lymphoproliferative lesions were either reticulum cell sarcoma (RCS) type A or reactive lymphoid hyperplasia (RLH). RCS occurred in 29/77 G_{ix} * F_1 mice, as opposed to 4/33 G_{ix} * F_1 , 2/25 B6- G_{ix} * and 0/22 129 mice. RLH occurred in 8 G_{ix} * F_1 mice but not in the other strains. In addition to G_{ix} antibody, the G_{ix} * F_1 mice produced antibodies to G antigens related to xenotropic and to ecotropic MuLV's, natural thymocytotoxic autoantibody, and antinuclear antibodies were produced by G_{ix} * F_1 mice. However, these four antibodies were also found in the other strains. It is concluded that the chronic production of G_{ix} antibody may be necessary for the

development of severe glomerulonephritis and for the increased occurrence of lymphoproliferative diseases in G_{ix} * F_1 mice. (23 refs)

- 79-7098 HLA System and Testicular Germinative Tumours. (Eng) Majsky, A. (Inst. Hematology and Blood Transfusion, U nemocnice 1, 128 20 Prague, Czechoslovakia); Abrahamova, J.; Korinkova, P.; Bek, V. *Oncology* 36(5): 228-231; 1979.

The frequency of 23 HLA antigens of the A and B loci was compared in 62 patients with testicular germinative tumors (40 with seminomas and 22 with nonseminomas) and 301 healthy unrelated subjects. The frequencies of HLA-A3, A10, B14, B40, and Bw35 antigens were increased in the seminoma patients, while A2 and B15 were decreased. Only the increase in Bw35 was statistically significant, but after correction, the result was no longer significant. In the nonseminoma patients (10 embryonal carcinomas, 5 teratocarcinomas, and 7 mixed forms), the frequency of HLA-A10, B18, B40, and Bw21 antigens was increased, and the frequency of B8 and B17 was decreased. The only statistically significant increase was that of the A10 antigen, but after correction the result was not significant. The 5-yr survival rate was higher in nonseminoma patients who had no HLA-A2, A9, A10, Aw19, B5, B12, B13 and Bw21 antigens. (28 refs)

See also:

- *(Rev.): 79-6608.
 *(Chem.): 79-6645, 79-6650, 79-6789, 79-6796, 79-6829.
 *(Phys.): 79-6878, 79-6879, 79-6887, 79-6906, 79-6907, 79-6909, 79-6914, 79-6916.
 *(Viral): 79-6935, 79-6942, 79-6951, 79-6952, 79-6955, 79-6959, 79-6960, 79-6967, 79-6971, 79-6977, 79-6980, 79-6981, 79-6983, 79-6987, 79-6988, 79-6995, 79-7009, 79-7013, 79-7015, 79-7018, 79-7028, 79-7030, 79-7047, 79-7048, 79-7049, 79-7053, 79-7059, 79-7061.
 *(Path.): 79-7117, 79-7118.
 *(Epid.-Biom.): 79-7149, 79-7155.

PATHOGENESIS

- 79-7099 The Karyotype of Meningioma. (Ger) Zankl, H. (Institut für Humangenetik, Universität Saarlandes, W. Germany). *Veroeff Pathol* 111: 86 pp.; 1979.

A cytogenetic study of 140 meningiomas was performed. All cells or at least one cell line showed a partial or total G-monosomy (monosomy 22) in 72% of the tumors. After chromosome 22, the chromosomes 1, 13-15, 18, and the sex chromosomes were lost most frequently. Uniform karyotype was found in about 50% of all tumors, while two or more cell lines were seen in the others. In many cases it was obvious that multiple lines had arisen from one stemline. The most frequent mosaic in the same tumor (24 cases) was composed of cells with normal and 22-monosomic karyotypes. Structural chromosome aberrations, occurring regularly in all mitoses or at least in one cell line, were observed in 32 tumors; in 10 of these, one chromosome 1 showed a structural aberration. The long arm of chromosome 22 was deleted in 5 cases, the remaining fragment resembling the Philadelphia chromosome. Breaks were seen in 17.5% of the mitoses. Chromosomes 1 and 2 were affected more frequently than expected, whereas chromosomes of the C group showed very few breaks. Dicentric chromosomes were found mostly in chromosomes of group F. The frequencies of breaks and dicentric chromosomes showed a reverse correlation to the grade of hypodiploidy in the tumor mitoses. Typical in vitro growth of the more hypodiploid tumors contrasted with that of the meningiomas with normal karyotype and with monosomy 22, which showed a similar proliferation under tissue culture conditions. Tumors infiltrating the skull and recurrent tumors often showed a higher degree of hypodiploidy or an atypical chromosome loss. In nearly all meningiomas localized in the convexity of the cerebrum, a higher degree of hypodiploidy was observed. With only a few exceptions, the tumors of the spinal canal showed a monosomy 22, whereas those of the basis encephali had mostly normal karyotypes. While the male:female ratio in the entire series was 3:2, meningiomas with a higher degree of hypodiploidy or atypical chromosome loss were found in women as often as in men; and 75% of the tumors with normal or 22-monosomic karyotype occurred in women. (248 refs)

- 79-7100 Hereditary Retinoblastoma: Host Resistance and Age at Onset. (Eng) Matsunaga, E. (Dept. Human Genetics, Natl. Inst. Genetics, 411 Mishima, Shizuoka-ken, Japan). *J Natl Cancer Inst* 63(4): 933-939; 1979.

Age-specific incidence data from 244 bilateral and 31 unilateral cases of hereditary retinoblastoma were analyzed. In the bilateral cases, there was a high correlation between the age of the patient at diagnosis in one eye with that in the other, suggesting that age at onset is largely determined by host factors common to both eyes. The mean ages of all patients at diagnosis varied consistently with the parental phenotype, suggesting that inherited host resistance plays an important role in the latency period. (27 refs)

- 79-7101 Absence of Chromosome Breakage in Patients with Retinoblastoma. (Eng) Knight, L. A. (Div. Cytogenetics, Dept. Pathology, Toronto General Hosp. and Univ.

Toronto, Toronto, Canada); Gardner, H. A.; Gallie, B. L. *Hum Genet* 51(1): 73-78; 1979.

To investigate the role of chromosome fragility in retinoblastoma (RB), peripheral blood lymphocytes from 12 patients with RB and 12 matched controls were studied. The frequency of chromatid and isochromatid aberrations was 5.6% of 763 cells from the RB patients and 7.3% of 423 cells from the controls. The frequencies of gaps and breaks in the RB patients were 3.4% and 1.7%, respectively; the frequency of breaks and fragments and translocations was 2.3%. In controls, the corresponding frequencies were 5.5%, 1.2%, and 1.4%, respectively. The results in RB patients did not differ significantly from those in controls. In only one instance was the frequency of breaks greater in an RB patient than in his control, and no significant difference was found between a similarly treated twin brother with RB and his control. Thus, RB is not associated with a spontaneous increase in chromosome fragility. (7 refs)

- 79-7102 New Findings in the Chromosome 13 Long-Arm Deletion Syndrome and Retinoblastoma. (Eng) Weichselbaum, R. R. (Harvard Medical Sch., Peter Bent Brigham Hosp., Boston, MA); Zakov, Z. N.; Albert, D. M.; Friedman, A. H.; Nove, J.; Little, J. B. *Ophthalmology (Rochester)* 86(6): 1191-1198; 1979.

The case reports are presented of three patients with ocular abnormalities or retinoblastoma associated with deletion of the long arm of chromosome 13 (13q-). Two patients had colobomas of the choroid as well as optic nerve hypoplasia and retinal dysplasia, both confirmed histologically; the third patient had retinoblastoma. Fibroblast radiosensitivities were examined in patients with sporadic and familial retinoblastoma and in the three patients reported here. Fibroblasts from patients with hereditary retinoblastoma were more radiosensitive than those from patients with sporadic retinoblastoma. Fibroblasts from the two patients with 13q- but without retinoblastoma showed radiosensitivity comparable to that of normal controls, while the patient with chromosome deletion and retinoblastoma showed significantly greater radiosensitivity than the normal controls. Increased radiosensitivity in patients with hereditary retinoblastoma may suggest a defect in a molecular DNA repair process. (28 refs)

- 79-7103 Metastatic Squamous Cell Carcinoma of the Lip. Occurrence in Blacks with Discoid Lupus Erythematosus. (Eng) Martin, S. (Dept. Dermatology, Baylor Coll. Medicine, Houston, TX); Rosen, T.; Locker, E. *Arch Dermatol* 115(10): 1214; 1979.

The development of squamous cell carcinoma of the lip in two black patients with chronic discoid lupus erythematosus (DLE) of the face and lip is reported. A 62-yr-old man with a 14-yr history of DLE developed a well-differentiated squamous cell carcinoma on the right side of the upper lip followed 2 yr later by fatal adrenal, hepatic, and bone marrow metastases. A 54-yr-old man

with an 18-yr history of DLA developed a poorly differentiated squamous cell carcinoma of the entire lower lip. Lymphatic metastases were also found on both sides of the neck. Enhanced metastatic potential may be present when squamous cell carcinoma arises in DLE of the lips. (6 refs)

- 79-7104 Malignant Fibrous Histiocytoma Arising in a Patient with Multiple Neurofibromatosis: A Case Report and a Literature Review. (Eng) Johnson, P. S. (Div. Hematology-Oncology, Dept. Internal Medicine, Univ. Iowa, Iowa City, IA 52240); Katz, D. A.; Pester, J.; Penn, R. *J Surg Oncol* 12(2): 97-105; 1979.

The case is reported of a 56-yr-old man with the characteristic clinical and histologic features of multiple neurofibromatosis. The patient also had a malignant fibrous histiocytoma involving the right thigh with metastasis to the lung. A definite association between Von Recklinghausen's disease and various sarcomas (most commonly neurofibrosarcomas) of the peripheral nerves and the somatic soft tissues is well-known. This is apparently the first report in the literature of a malignant fibrous histiocytoma arising in a patient with multiple neurofibromatosis. The phenomenon of sarcomatous change in Von Recklinghausen's disease and the clinical and pathologic features of malignant fibrous histiocytoma are discussed. (37 refs)

- 79-7105 Non-Hodgkin's Lymphoma and Acute Myeloblastic Leukemia. A Report of 12 Cases and Review of the Literature. (Eng) Zarrabi, M. H. (Veterans Admin. Medical Center, Northport, NY 11768); Rosner, F.; Bennett, J. M. *Cancer* 44(3): 1070-1080; 1979.

Twelve cases of non-Hodgkin's lymphoma and acute myeloblastic leukemia or one of its variants are reported, and an additional 33 cases from the literature are reviewed. The mean interval between the diagnoses of lymphoma and acute leukemia is 5.2 yr. In five patients the two diseases occurred simultaneously or within 6 mo of each other. All but 10 of the 45 patients received radiation therapy for their lymphoma. Nine patients had either total nodal or total body irradiation or both. Eight patients received chemotherapy alone. No patient was untreated. Survival after the diagnosis of acute leukemia ranged from 3 days to 14 mo, with a median of 3 mo. Four patients achieved complete hematological remission following antileukemic therapy. Acute leukemia is estimated to occur in patients with non-Hodgkin's lymphoma in New York State with a 37-fold increased frequency over the expected number. Although such an increase over expected frequency may be attributed to the increased risk of a second neoplasm in patients with a primary tumor, it seems more likely that the acute leukemia may be related to the radiotherapy and/or chemotherapy administered to treat the lymphoma. However, late death from leukemia after chemotherapeutic or radiotherapeutic remission of advanced non-Hodgkin's lymphoma is preferable to morbidity and/or early death from untreated or inadequately treated lymphoma. (67 refs)

- 79-7106 The 5q- and Additional Chromosome Anomalies in Two Patients with Acute Myeloid Leukemia. (Eng) Petit, P. (Dept. Cytogenetics, CDH, Ch. D'Alsemberg 196, B-1180 Brussels, Belgium); Van den Berghe, H. *Ann Genet (Paris)* 22(2): 103-105; 1979.

Two elderly women with acute myelogenous leukemia were found, upon initial marrow and unstimulated blood examination, to have deletions of the long arm of chromosome number 5 (5q-) and other chromosome anomalies. An 83-yr-old patient with a modal chromosome number of 46 also had a terminal deletion of chromosome 12. An 81-yr-old patient had a modal chromosome number of 43; chromosomes 7, 12, and 18 were missing. In addition to the 5q-anomaly, there was an acrocentric marker consisting of chromosome 21 bearing translocations on its long arm of part of the long arms of chromosomes 7 and 12. In each patient, the same anomalies were present in bone marrow and blood cells. (9 refs)

- 79-7107 "Pre-B" Phenotypes in Blast Crisis of PH⁺ Positive CML: Evidence for a Pluripotential Stem Cell "Target". (Eng) Greaves, M. F. (Membrane Immunology Lab., Imperial Cancer Res. Fund, London, England); Verbi, W.; Reeves, B. R.; Hoffbrand, A. V.; Drysdale, H. C.; Jones, L.; Sacker, L. S.; Samarasingha, I. *Leuk Res* 3(4): 181-187, 189-191; 1979.

Six patients with Philadelphia chromosome (Ph⁺)-positive acute leukemia and 20 patients with chronic myeloid leukemia (CML) in blast crisis were tested with a panel of immunological, enzymatic, and histochemical markers and for the presence of cytoplasmic Ig-M as an indicator of the earliest detectable cells in the B cell lineage (pre-B cells). Routine blood preparations from all patients had >25% blast cells. Nineteen patients had the phenotype common (c) to acute lymphoblastic leukemia (ALL) which included the cALL gp100 membrane antigen and terminal deoxynucleotidyl transferase. Three of these 19 patients, all of whom had CML in blast crisis, had leukemic cells with a pre-B phenotype (staining with anti-IgM). In two cases, >75% of lymphoblasts contained cytoplasmic IgM, but no cell surface immunoglobulin was present. Two other patients with CML in blast crisis had 5% IgM-positive cells. These findings indicate that Ph⁺ with a typical translocation onto chromosome 9 can penetrate into the B cell lineage and that clonal evolution in CML can involve selective growth of cells with an apparent maturation arrest in the early B cell compartment. These data provide evidence for the existence of a common lymphoid-myeloid pluripotential stem cell in humans, which might be the target for the Ph⁺ alteration and leukemia initiation in at least some patients with CML. (32 refs)

- 79-7108 Chromosomes and Causation of Human Cancer and Leukemia. XXXIV. A Case of "Hypereosinophilic Syndrome" with Unusual Cytogenetic Findings in a Chloroma, Terminating in Blastic Transformation and CNS Leukemia. (Eng) Huang, C. S. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Gomez, G. A.; Kohno, S. I.; Sokal, J. E.; Sandberg, A. A. *Cancer* 44(4): 1284-1289; 1979.

The case report of a patient in whom the "hypereosinophilic syndrome" terminated in a frank leukemic condition with an extramedullary granulocytic sarcoma (chloroma) and leukemic CNS involvement is presented. The patient, a 46-yr-old white man, developed massive hepatosplenomegaly, a pleural effusion, leukocytosis, and a left parasternal mass following relatively symptom-free persistent hypereosinophilia for about 5 yr. Bone marrow aspiration and biopsy and peripheral blood differential showed eosinophilia and a shift to the left with immature cells. A high serum vitamin B₁₂ level and a leukocyte alkaline phosphatase score of 0 were found. Biopsy of the soft tissue mass revealed a

chloroma with a hyperdiploid karyotype (49,XY,+10,+15+19,3q-), whereas the bone marrow cells had a normal male karyotype. The patient responded temporarily to chemotherapy but eventually developed CNS leukemia and died in the blastic phase of the disease. It is possible that this case represents a variant of Ph⁺-negative chronic myelocytic leukemia to which the term "chronic eosinophilic leukemia" could be applied. (30 refs)

- 79-7109 Leukemia in a Black Child with Bloom's Syndrome. Somatic Recombination as a Possible Mechanism for Neoplasia. (Eng) Festa, R. S. (Div. Oncology, Children's Hosp. Philadelphia, 34th and Civic Center Blvd., Philadelphia, PA 19104); Meadows, A. T.; Boshes, R. A. *Cancer* 44(4): 1507-1510; 1979.

The case report of a 5-yr-old black child with Bloom's syndrome and acute lymphocytic leukemia (ALL) is presented. The patient's skin had adjacent areas of decreased and increased pigmentation similar to "twin-spots", a manifestation of somatic cell DNA recombination, seen in *Drosophila*. Their presence provides evidence that clones of cells in Bloom's syndrome have become homozygous for a particular gene. Somatic cell recombination is proposed as a mechanism to explain the increased incidence of neoplasms in Bloom's syndrome and supports the hypothesis that cancer may be a recessive disorder at the cellular level. (25 refs)

- 79-7110 Epidemiology of Nodular Paragranuloma (Hodgkin's Disease with Lymphocytic Predominance, Nodular). (Eng) Poppema, S. (Pathologisch-Anatomisch Laboratorium der Rijksuniversiteit, Oostersingel 63, NL-9713 EZ Groningen, Netherlands); Kaiserling, E.; Lennert, K. *J Cancer Res Clin Oncol* 95(1): 57-63; 1979.

The age and sex distribution and the localization of excised lymph nodes of 206 patients with a nodular variant of Hodgkin's disease with lymphocytic predominance, termed nodular paragranuloma, are presented and compared with data on other types of Hodgkin's disease. The age curve of nodular paragranuloma showed a peak in the fourth decade, which was clearly separated from the peak in the third decade exhibited by the nodular sclerosis type of Hodgkin's disease and from the peak in the sixth and seventh decades of the mixed cellularity type. The peak in the age curve of nodular paragranuloma resulted from the high frequency in men in the fourth decade; the female age curve had no peaks. The overall male-to-female ratio was 2.4:1. The age and sex distribution of diffuse paragranuloma was nearly identical to that of nodular paragranuloma, whereas the age and sex distribution for other lymphocytic predominance types resembled that of the mixed cellularity type. These data indicate that the lymphocytic predominance type of Hodgkin's disease is not a uniform group and support the view that paragranuloma is a separate entity. Differences in localization of excised lymph nodes among the various types of Hodgkin's disease were noted but were considered to be of little significance. (11 refs)

- 79-7111 Mycosis Fungoides and Hodgkin's Disease Occurring in the Same Patient: Report of Three Cases. (Eng) Chan, W. C. (Dept. Pathology, Univ. Chicago, 950 E. 59th St., Chicago, IL 60637); Griem, M. L.; Grozea, P. N.; Freel, R. J.; Variakojis, D. *Cancer* 44(4): 1408-1413; 1979.

The occurrence of the nodular sclerosing type of Hodgkin's Disease (HD) in three patients with typical mycosis fungoides (MF) is reported. All three patients had a long history (8-15 yr) of MF skin lesions. In two patients, a 62-yr-old white man and a 53-yr-old white man, the disease followed a steady progression from initial erythematous scaly lesions to the development of plaques, and, eventually, to skin tumors. The diagnosis of HD was made 2 yr after the diagnosis of MF on the basis of skin biopsies. In the third patient, a 46-yr-old black man, small erythematous papules gradually evolved into small plaques. The histological diagnoses of MF and HD were made simultaneously. It is possible that some of the previously described cases of MF reported to have transformed into HD could be examples of these two lymphomas occurring in the same patient. (28 refs)

- 79-7112 Fatal Lymphoma after Transplantation of Cultured Thymus in Children with Combined Immunodeficiency Disease. (Eng) Borzy, M. S. (Dept. Pediatrics, Univ. Wisconsin, Madison, WI); Hong, R.; Horowitz, S. D.; Gilbert, E.; Kaufman, D.; DeMendonca, W.; Oxelius, V. A.; Dictor, M.; Pachman, L. *N Engl J Med* 301(11): 565-568; 1979.

A fatal, widespread, polyclonal, B-cell immunoblastic lymphoproliferative disorder that developed in three children (a 1-yr-old boy, a 3-yr-old girl, and a 4-yr-old boy) with combined immunodeficiency shortly after intraabdominal transplantation of cultured thymus epithelium for immunoreconstitution is described. All three patients had surface immunoglobulin-bearing cells (15%-20%) in the peripheral blood before transplantation and polyclonally elevated immunoglobulins afterward. Abnormal immunoregulation was demonstrated in all patients before transplantation by a lack of Concanavalin A-induced suppressor-cell activity in mixed leukocyte culture; this persisted in two patients after transplantation. The transplant may have acted as a promoter through immunostimulation or production of promoter factors; excessive polyclonal B-cell proliferation may have resulted because of inadequate immunoregulatory mechanisms. On the basis of experience with 30 patients with various immunodeficiency diseases, the incidence of this complication is approx 10% (3/30). (28 refs)

- 79-7113 Granulocytic Sarcoma Preceding Acute Leukemia. A Report of Six Cases. (Eng) Krause, J. R. (Central Hematology, Presbyterian-Univ. Hosp., Pittsburgh, PA 15213). *Cancer* 44(3): 1017-1021; 1979.

A 16-yr-old boy presented with granulocytic sarcoma in a pericardial effusion following trauma and preceding acute myelogenous leukemia (AML) by 8 mo. At the time of original diagnosis, four bone marrow aspirations and needle biopsy specimens all showed a normocellular marrow; repeat blood counts were also normal. Eight mo later, blood and marrow counts indicative of AML were observed. A review of the surgical files of one hospital for a 20-yr period revealed five additional cases of granulocytic sarcoma preceding AML by 1.5 to 9 mo. When presenting in an extramedullary site, especially preceding peripheral blood and bone marrow manifestations of leukemia, a misdiagnosis of histiocytic lymphoma may result. Although these six cases represent a very small series, the most recent cases have shown induction/remission and survival characteristics like those of AML patients without granulocytic sarcoma. (22 refs)

- 79-7114 Primary Amyloidosis, Pure Red Cell Aplasia, and Kaposi's Sarcoma in a Single Patient. (Eng) Shimm,

D. S. (Dept. Medicine, Duke Univ. Medical Center, Durham, NC); Logue, G. L.; Rohlfing, M. B.; Gaede, J. T. *Cancer* 44(4): 1501-1503; 1979.

The occurrence of Kaposi's sarcoma, pure red cell aplasia, and primary amyloidosis in a 53-yr-old black man is reported. Immunologic abnormalities associated with abnormal B-cell function and humoral immunity included marrow plasmacytosis, antinuclear antibodies, heterogeneous hyperglobulinemia followed by a small IgG kappa paraprotein, and Bence Jones proteinuria. The patient was able to convert his PPD skin test, indicating that other T-cell functions were intact. The abnormalities in B-cell function were not global, since IgM and IgA levels were normal and he did not suffer from recurrent bacterial infections. This case represents an interesting conjunction of three diseases, all of which are associated with an abnormal immunologic state. (20 refs)

- 79-7115 Ultrastructure of Telangiectatic Osteosarcoma. (Eng) Roessner, A. (Inst. Pathology, Univ. Munster/Westf., Westring 17, D-4400 Munster, W. Germany); Hobik, H. P.; Immenkamp, M.; Grundmann, E. *J Cancer Res Clin Oncol* 95(2): 197-207; 1979.

The features observed in tissue samples from two telangiectatic osteosarcomas (TOS) examined by light and electron microscopy are described. Samples were obtained from the excised tumors of two boys (15 and 17 yr old); diagnosis of TOS was based on clinical, radiologic, and histologic features. The microscopic findings were similar for both patients. Light microscopy revealed that most tumor areas were composed of cystic spaces filled with clotted blood and segmented by thin septa. Solid areas where osteoid production was more pronounced were composed of densely-packed cells with irregularly shaped nuclei. Clusters of anaplastic tumor cells were sometimes noted. Electron microscopy revealed osteoblast-like tumor cells, spindle-shaped cells of fibroblastic origin, anaplastic-type tumor cells, and chondroblast-like tumor cells. Also observed were endothelial cells that were connected by tight intracellular junctions and that surrounded erythrocytes to form small capillaries. These endothelial cells contained pinocytotic vesicles, large numbers of fine fibrils, small amounts of granular and agranular endoplasmic reticulum, well developed Golgi bodies, and cytoplasmic organelles that resembled the rod-shaped inclusion bodies of the Weibel-Palade type. The characteristics of these cells indicated that they were angiosarcomatous components, suggesting that a multipotent mesenchymal cell with a capacity for differentiation to osteoblast-like, fibroblast-like, chondroblast-like, and angioblastic cells may be the cell of origin in TOS. (12 refs)

- 79-7116 Osteogenic Sarcoma in Siblings. (Eng) Colyer, R. A. (Dept. Orthopedic Surgery, Indiana Univ. Sch. Medicine, 1100 W. Michigan St., Indianapolis, IN 46223). *Johns Hopkins Med J* 145(3): 131-135; 1979.

A brother and sister with osteogenic sarcoma are described. The sister (aged 16 yr) presented with a 2-mo history of shoulder pain. The microscopic findings in a biopsy specimen were consistent with a diagnosis of osteogenic sarcoma, which agreed with the radiologic findings. Despite amputation and chemotherapy, pulmonary metastasis appeared, and the patient died following surgical removal of the metastasis and further chemotherapy. The brother presented with knee pain of 5-mo duration at 11 yr of age. Osteogenic sarcoma was diagnosed, but the family refused all

treatment and the patient died with pulmonary metastasis 8 mo later. A review of the literature revealed an additional 30 cases of osteogenic sarcoma in 13 families. Twenty-two involved siblings, two father-daughter pairs, and the rest were more distantly related. The evidence that genetic factors play an etiologic role in osteogenic sarcoma is substantial, but environmental factors may also be involved. (28 refs)

- 79-7117 Growth of Osteoid Osteoma Transplanted into Athymic Nude Mice. (Eng) Urist, M. R. (UCLA Bone Res. Lab., 1000 Veteran Ave. A3-34, Los Angeles, CA 90024); Lindholm, T. S.; Mirra, J. M.; Grant, T. T.; Finerman, G. A. *Clin Orthop* (141): 275-280; 1979.

An osteoid osteoma was excised from the neck of the femur of a 23-yr-old man and cut into four 1.5-mm³ fragments for immediate transplantation into muscle pouches of athymic nude mice. One fragment was devitalized by lyophilization prior to implantation. The viable tumor cell xenografts grew, differentiated into uncanceled osteoid, and retained the characteristics of the original tumor. The killed implants were resorbed, but both the surviving viable and nonviable tumor tissue induced the connective tissue cells of the mouse host bed to proliferate and differentiate into normal cartilage and calcified bone. The mouse new bone deposits were remodeled and colonized by bone marrow, a tissue not seen in osteoid osteomas. These observations suggest that the sclerotic bone shell characteristic of osteoid osteomas may represent an inductive reaction of host bed tissue to an osteoma cell product comparable to the bone morphogenetic protein produced by normal bone cells and transferred by normal bone matrix. (29 refs)

- 79-7118 Production of Mesenchymal Tumors in Nude Mice Using Ph¹ Negative "Fibroblasts" Obtained from a Ph¹ Positive CML Patient and Other Human Sources. (Eng) Wilson, F. D. (Radiobiology Lab., Sch. Veterinary Medicine, Univ. California, Davis, CA 95616); Greenberg, B. R.; Spangler, W. L.; Shifrine, M.; Gershwin, M. E.; Klein, A. K. In: *Hematopoietic Cell Differentiation. Proceedings of the ICN-UCLA 1978 Symposium on Molecular and Cellular Biology held in Keystone, CO, 10 March 1978*. Golde, D. W.; Cline, M. J.; Metcalf, D.; Fox, C. F., eds. (New York: Academic Press) Vol. 10, 504 pp.; 231-240; 1978.

The development of a model system for investigating the role of hematopoietic stromal elements in the regulation of hematopoiesis and in the pathogenesis of myelofibrosis is reviewed. The model involves the selection of fibroblastic adherent cells from human bone marrow samples and the subsequent inoculation of these cells into nude mice. The fibroblastic cells had normal karyotypes, whether they were isolated from a patient with Philadelphia chromosome (Ph¹)-positive chronic myelogenous leukemia (Ph¹ + CML), from a male patient who had received a bone marrow transplantation from his sister and so represented a male-female hematopoietic chimera, or from normal volunteers. Mesenchymal tumors resulted from the injection of fibroblastic elements using adherent cells from all three sources. The tumors were composed of cells with fibroblastic to reticuloendothelial morphology and were not observed for more than 1 wk. There were no morphological or behavioral differences among mesenchymal tumors produced with CML, chimeric, or normal human sources. The results of these studies suggest that the adherent populations forming in bone marrow are not related to hematopoietic stem cells and contain stromal cell capacities when transplanted in vivo regardless of their

in vitro morphologies. The results in the nude mice establish the feasibility of using the transplantation model for investigating the pathogenesis of myelofibrosis associated with myeloproliferative disorders. (22 refs)

- 79-7119 The Histogenesis of Small-Cell Bronchial Carcinoma. (Ger) Raikhlin, N. T. (Abt. Pathomorphologie der Geschwulste des Menschen, Onkologisches Forschungszentrum, Kaschirskoje Chaussee 6, 115478 Moscow, USSR); Warzok, R.; Smirnowa, E. A. *Zentralbl Allg Pathol* 123(3): 202-209; 1979.

Electron microscopy (EM) revealed both neurosecretory granules (NSG) and multilamellar bodies (MLB) in a lung tumor which had the typical appearance of a small-cell (ie, oat cell) carcinoma by light microscopy. The latter technique revealed an apparently homogeneous small-cell carcinoma with dense nuclei often toward one end of the cell. The finding of NSG, considered typical of small-cell carcinoma, and MLB, characteristic of adenocarcinomas of the lung, both in the same tumor cell suggests that these types of lung carcinomas can originate from one type of pluripotent cell. The tumor, found in an upper pulmonary lobe of a 52-yr-old woman, was immediately fixed in glutaraldehyde for EM study. Anaplastic cells with large nuclei and few organelles were found, as were relatively differentiated cells with numerous mitochondria, polysomes, and endoplasmic reticulum. Transition forms between these two cell types were identified. The intracytoplasmic lamellar bodies were osmiophilic. Some cells contained only NSG or MLB, but usually both were found in one and the same cell. (34 refs)

- 79-7120 Role of Tumor Thromboplastin in the Mode of Distribution of Metastatic Foci in the Lung. (Eng) Kohga, S. (Dept. Pathology, Kyushu Univ., Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan); Tanaka, K. *Gann* 70(5): 615-619; 1979.

Experiments were carried out to determine the role of tumor thromboplastin and the distribution of metastatic lesions in the lung. Crude tumor cell extract from rat ascites hepatoma AH130 had a clotting time of 14 sec compared with 19.5 sec for normal rat brain extract. The iv injection of this tumor extract in male Donryu rats caused thrombus formation in the capillaries, arterioles, and arteries of the lungs of rats killed 3 min or 72 hr after injection. Groups of six rats each received 0.2 ml tumor extract or saline followed immediately by 1×10^7 AH130 tumor cells iv. The rats were killed 3 min, 24 hr, or 72 hr after inoculation. Rats injected with tumor cell extract followed by tumor cells also showed thrombus formation in the capillaries, arterioles, and lung arteries, while the rats sacrificed 3 min after saline or tumor cell injection revealed widespread small thrombus formation, mainly in the capillaries and arterioles. After 72 hr, the number of metastatic foci in the lungs of the group pretreated with tumor cell extract was less than that in the group pretreated with saline. The size of metastatic foci in the alveolar septa in both groups was alike, but there was metastasis formation in the larger pulmonary arteries in the group pretreated with tumor cell extract but not with saline. These large metastatic foci were composed of tumor cells and various amounts of fibrin thrombi. These results suggest that tumor thromboplastin may play a role in the mode of distribution of metastatic foci in the lung. (17 refs)

- 79-7121 Carcinoma Arising in the Wall of Congenital Bile Duct Cysts. (Eng) Todani, T. (Dept. Surgery, Okayama Univ. Medical Sch., 2-5-1 Shikatacho, Okayama City

700, Japan); Tabuchi, K.; Watanabe, Y.; Kobayashi, T. *Cancer* 44(3): 1134-1141; 1979.

Four cases of carcinoma arising in a choledochal cyst are presented, and an additional 59 cases are reviewed from the literature. Three of four patients (3 women, 1 man, 17-26 yr old) had histologically verified adenocarcinomas arising from choledochal cysts; the fourth patient's tumor was a squamous cell carcinoma. The three patients with adenocarcinomas also had liver metastases, while the squamous cell carcinoma had spread widely to the neighboring retroperitoneum. Among the 63 patients reviewed, the ages ranged from 15 to 73 yr, and 42 of them were under 36 yr of age; thus, the average was several decades younger than that seen in extrahepatic carcinoma patients without bile duct cyst involvement. The female:male ratio in the 63 cases was 2.5:1, in contrast to a male predominance usually seen in carcinoma without bile duct cysts. The series included 42 Japanese patients and 36 patients who had undergone various internal drainage procedures (choledochocystoduodenostomy in 19, choledochocystojejunostomy in 6, and bile duct drainage in 11). Even with primary excision of the cyst, carcinoma could still arise from the retained bile duct or from intrahepatic cysts. Nine cases have been reported of patients with bile duct cysts who developed carcinoma in the liver, pancreas, pancreatic duct, or bile duct; thus the presence of congenital bile duct cysts may predispose to carcinomas throughout the hepatobiliary system. (26 refs)

- 79-7122 Analysis of Chromosomal Proteins of Fractionated Chromatin from Rat Liver and Transplantable Hepatocellular Carcinomas. (Eng) Rodriguez, L. V. (Dept. Pathology, Section Experimental Pathology, Univ. Texas System Cancer Center, Houston, TX 77030); Klein, K. K.; Amoroso, M.; Becker, F. F. *Int J Cancer* 24(4): 490-497; 1979.

The chromosomal proteins from a number of transplantable hepatocellular carcinomas (THC) induced by N-acetylaminofluorene or analogues of fluorenylacamide and showing great variations in growth rate were examined by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Chromatin from hepatomas and from normal and regenerating livers of male Buffalo rats were fractionated into rapidly and slowly sedimenting gradient components. Ten nonhistone chromosomal proteins (NHCP) present in the tumors and ranging in mol wt from 220,000 to 55,000 were absent from normal liver. Also, each rapidly growing tumor possessed more nonhistone protein bands in the most rapidly sedimenting chromatin fractions than did the corresponding slowly growing tumor fractions. A number of single proteins common only to normal liver and/or rapidly or slowly growing tumors were also found. In contrast, NHCP banding patterns of rapidly growing 70% hepatectomized rat liver were identical to those of nondividing liver. The prototypic "minimal deviation tumor" (9618A) varied more in its NHCP-banding pattern when compared to liver than did rapidly growing, poorly differentiated tumors. (41 refs)

- 79-7123 Sequential Analysis of Hepatic Carcinogenesis: The Comparative Architecture of Preneoplastic, Malignant, Prenatal, Postnatal and Regenerating Liver. (Eng) Ogawa, K. (Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada, M5G 1L5); Medline, A.; Farber, E. *Br J Cancer* 40(5): 783-791; 1979.

The structural patterns of hepatocytes in early and late preneoplastic foci and nodules were compared with those in hepatocarcinomas, developing fetal and neonatal liver, and

regenerating liver. Hepatocytes were obtained from male Fischer-344 rats in which hyperplastic lesions were induced by diethylnitrosamine (200 mg/kg, ip) followed 2 wk later by 2-acetylaminofluorene (0.02% of the diet for 2 wk). The hepatocytes in hyperplastic lesions were arranged in plates two or more cells thick and in glands. They showed unusual separation from each other, with irregularly dilated bile canaliculi. Hepatocytes from normal adult liver were arranged only in one-cell-thick plates. The organizational pattern in the hyperplastic lesions resembled that in developing liver in the perinatal period, that in regenerating liver following the peak of cell division, and that in some hepatocellular carcinomas. However, the resemblance to developing and regenerating liver was incomplete, failing to reproduce exactly the characteristics of the normal tissues. Unlike the normal tissues, in which there was a highly predictable time scale for change, an apparent delay or interruption in maturation was observed in the hyperplastic lesions. This delay or interruption may be of importance in lesions that persist and ultimately evolve into hepatocellular carcinomas. (21 refs)

- 79-7124 Familial Islet Cell Tumors in Von Hippel-Lindau's Disease. (Eng) Hull, M. T. (Dept. Pathology, Indiana Univ. Sch. Medicine, 1100 W. Michigan, Indianapolis, IN 46202); Warfel, K. A.; Muller, J.; Higgins, J. T. *Cancer* 44(4): 1523-1526; 1979.

A family with well-documented Von Hippel-Lindau disease in four siblings, all of whom developed neoplasms, is reported. Three had cerebellar hemangioblastomas, two had retinal hemangioblastomas, and all four had pheochromocytomas; all of these neoplasms are characteristic of the disease. Additionally, two patients developed islet cell tumors of the pancreas, one in one patient and five in the other. Although a familial incidence of islet cell tumors is known in multiple endocrine adenomatosis, type 1 and Zollinger-Ellison syndrome, such a familial occurrence has been heretofore unrecorded in the Von Hippel-Lindau complex. (26 refs)

- 79-7125 The Fine Structure of Pancreatic Duct Neoplasm in Syrian Golden Hamsters. (Eng) Althoff, J. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany); Wilson, R. B.; Ogrowsky, D.; Pour, P. *Prog Exp Tumor Res* 24: 397-405; 1979.

Scanning and transmission electron microscopic observations of pancreatic neoplasm initiated or promoted by bis(2-hydroxypropyl)-N-nitrosamine (BHP), bis(2-acetoxypropyl)-N-nitrosamine (BAP), bis(2-oxopropyl)-N-nitrosamine (BOP), and N-nitroso-2,6-dimethylmorpholine (DMNM) in Syrian Golden Hamsters are presented. The main structural pattern of the pancreas is observed in fetal hamsters 3 days before delivery; within 4 wk of delivery, the acini grow to their normal size (38 x 27 µm). After treatment with nitroso compounds, acinar cell necrosis was seen in some cases, and other acini showed irregular formation of zymogen granules and an expanded rough endoplasmic reticulum. Mature islets of Langerhans (IL) are first observed 10 days after birth and enlarge throughout the following year. After treatment with nitroso compounds, the IL proliferated into small cystic channels lined with ductular epithelium; ductal and islet cells were connected by desmosomes. Periinsular duct formation also occurred. The lesions sometimes increased in size, compressing the remaining tissues and causing them to atrophy. Some cells exhibited

a single, centrally located cilium. The neoplastic foci underwent further alterations, such as ductular cuboidal and ductal columnar differentiation and atypia. Multifocal hyperplasia and proliferation of the ductular epithelium were observed concurrently with intra- and periinsular duct formation; this resulted in the development of an adenomatous pattern and the formation of benign adenomas surrounded by true and pseudocapsules. The luminal spaces were either lined by cuboidal single ciliated cells, columnar cells, or mixed-cell populations. The large ducts often showed hyperplastic epithelia as well as goblet cell metaplasia as early as 8 wk after initiation of treatment. A few weeks later, intraluminal proliferation showing papillary patterns and gland formation, eventually filling the lumen (dysplasia, carcinoma in situ, intraductal carcinoma) were observed. (8 refs)

- 79-7126 Aniridia-Wilms' Tumor Association: Evidence for Specific Deletion of 11p13. (Eng) Francke, U. (Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Holmes, L. B.; Atkins, L.; Riccardi, V. M. *Cytogenet Cell Genet* 24(3): 185-192; 1979.

The chromosomes of a 7-yr-old boy with aniridia, Wilms' tumor (WT), and mental retardation, previously reported as having an interstitial deletion of the short arm of chromosome 8 resulting from a t(8p+;11q-) translocation, were restudied with high-resolution trypsin-Giemsa banding of prometaphase chromosomes. The results revealed a complex rearrangement with four break points in 8p, 11p, and 11q, leading to a net loss of an interstitial segment of 11p, (region p1407 → p1304) but not of 8p. The patient's RBCs contained normal glutathione reductase (gene on 8p) and lactate dehydrogenase A (gene on 11p12) activities, indicating a gene dosage consistent with the chromosomal findings. The revised interpretation of this case agrees with those in seven others reported as having aniridia and interstitial 11p deletions. The data suggest that the distal half of band 11p13 is the site of gene(s) that lead to aniridia and predispose to WT and, to an even greater extent, mental retardation in the hemizygous state. (18 refs)

- 79-7127 Hereditary Renal-Cell Carcinoma Associated with a Chromosomal Translocation. (Eng) Cohen, A. J. (Dept. Renal Medicine, Univ. Massachusetts Medical Center, 55 Lake Ave. N., Worcester, MA 01605); Li, F. P.; Berg, S.; Marchetto, D. J.; Tsai, S.; Jacobs, S. C.; Brown, R. S. *N Engl J Med* 301(11): 592-595; 1979.

A family with renal-cell carcinoma and a constitutional chromosomal translocation is described. The cancer arose in five men and five women in three consecutive generations. The cancers produced symptoms in the proband and six relatives and was diagnosed in the three other relatives during screening of asymptomatic family members. The cancers tended to develop at earlier ages and to occur bilaterally and at several renal sites more frequently than do nonfamilial renal cancers. Karyotypes of the peripheral WBC of 22 adult family members showed that 10 had a balanced reciprocal translocation between chromosomes 3 and 8: 46 XY (or XX), t(3;8) (p21;q24). The other 12 subjects had normal karyotypes. The translocation was detected in all five family members who survived renal cancer and was assigned by pedigree analysis to three of the five who died from the disease. No family member with renal cancer had a normal karyotype. These findings provide karyotypic evidence that an inherited genetic abnormality predisposes humans to the development of a hereditary neoplasm. (21 refs)

- 79-7128 Prognostic Value of the Degree of Maturity and Histogenesis of Cancer of the Stomach. (Rus) Diksh-tein, E. A. (Dept. Pathologic Anatomy, M. Gorky Medical Inst., Donetsk, USSR); Vasilenko, I. V.; Shevchenko, N. I.; Merezko, V. A. *Arkhh Patol* 41(7): 25-32; 1979.

To evaluate the prognostic value of the degree of morphological differentiation, 110 specimens of stomach cancer were subjected to histological and histochemical examination. There were 46 specimens of adenocarcinoma and 64 specimens of poorly differentiated polymorphic cell or signet-ring cell carcinoma. Characteristic features of the poorly differentiated carcinomas were marked secretion of mucus and high activity of acid phosphatase, succinate dehydrogenase, and NAD-dependent malate dehydrogenase. In contrast, the adenocarcinoma cells showed high activity of NADP-dependent enzymes and less pronounced secretion of mucus. The results suggested a lower degree of cell differentiation (as opposed to histologic differentiation) and higher proliferative activity in the adenocarcinomas than in the undifferentiated carcinomas. The prognostic implications of the differences in cell and tissue differentiation between adenocarcinomas and undifferentiated carcinoma are discussed. (16 refs)

- 79-7129 Histogenesis of Carcinoma in the Glandular Stomach of the Rat After B I Resection. (Eng) Schlake, W. (Pathologisches Institut, Universität, Westring 17, 4400 Münster, W. Germany); Nomura, K. *Curr Top Pathol* 67: 1-67; 1979.

The histogenesis of carcinomas in the resected stomach was studied in Wistar rats subjected to gastric resection with subsequent Billroth-I gastroduodenostomy (OP) and treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the drinking water and/or antilymphocyte globulin. Carcinomas developed by week 104 in the animals subjected to OP only, by week 50 in animals subjected to OP and given MNNG starting 6 wk after surgery, and by week 104 in the animals subjected to OP and given MNNG starting 1 yr after surgery. Carcinoma development in the anastomosed mucosa followed two pathways: one via adenomatous polyps to fully developed polypous carcinoma; and the other via adenocystic gland proliferation to serosa-oriented, endophytic carcinoma. Changes in enzyme localization and activity occurred in preneoplastic and neoplastic tissues and also in areas of benign glandular regeneration. Chronic atrophic gastritis was constantly associated with all anastomosed mucosal tissues. Prolonged alterations such as enhanced proliferation and massive shifting or displacement of proliferative zones were found in the anastomosed mucosa as a result of severe imbalances in the interactions between differentiation and proliferation. These alterations appeared to be important pathogenic factors in the development of carcinomas in the resected stomach. The results illustrate the risk involved in Billroth-I surgery and the necessity for minimizing or preventing conditions predisposing to malignant transformation. (165 refs)

- 79-7130 Peutz-Jeghers Syndrome with Intestinal Carcinoma: Report of the Association in One Family. (Eng) Hsu, S. D. (Dept. Medicine, Div. Hematology-Oncology, Univ. Texas

Medical Branch, Galveston, TX); Zaharopoulos, P.; May, J. T.; Costanzi, J. J. *Cancer* 44(4): 1527-1532; 1979.

The occurrence of intestinal carcinoma in a 38-yr-old man and his father, both of whom had Peutz-Jeghers syndrome (PJS), is reported. The son had a grade III infiltrative rectosigmoid adenocarcinoma with widespread local extension to the pelvic organs and metastases to the peritoneum, liver, and lungs. Five elongated pedunculated smooth-surface polyps with the classical features of PJS hamartomas were also found in the ileum and transverse colon. While undergoing the 7th of 16 abdominal operations for removal of gastrointestinal polyps at the age of 49 yr, the father was found to have a large sessile polypoid carcinoma at the splenic flexure. Since PJS is inherited as an autosomal dominant trait, the detection of gastrointestinal malignancy in an affected individual might indicate that other family members with PJS might be at high risk for the development of gastrointestinal cancer. (12 refs)

- 79-7131 Spontaneous Adenocarcinoma of Gastrointestine in Rats. (Jpn) Miyamoto, M. (Dept. Pathology, Osaka Univ. Medical Sch., Osaka, Japan); Mizumoto, S.; Maeura, Y.; Utsunomiya, T.; Hashimoto, Z.; Tsujimura, T.; Tadokoro, T.; Takizawa, S. *Gan No Rinsho* 25(13): 1316-1319; 1979.

The occurrence of spontaneous gastrointestinal adenocarcinomas in inbred Wistar-Furth (WF) and MM rats is reported. Among 18th generation WF rats tumors were found in the ascending colon of 9 animals (5 males, 4 females), in the stomach of 5 (3 male, 2 female), and in the small intestines of 3 (1 male, 2 female). Tumors developed at all three sites in one 4-mo-old WF female. The colon cancers were more advanced than the gastric and small intestine tumors. The gastric tumors were characterized by thickening of the pyloric area and associated nodular eruptions, with occasional ulceration of the body of the stomach itself. Combined gastric and ileocolonic cancer was also observed in two 3-mo-old MM females of generations 1 and 4. Among 3-mo-old rats, ileocolonic tumors developed in two MM females of generations 2 and 3, a WF male and a WF female of generation 18, and one of the latter's female progeny. Colorectal tumors were seen in a 3-mo-old MM male of generation 0, a 10-mo-old MM female of generation 2, and a 4-mo-old inbred WF female. (6 refs)

- 79-7132 Familial Factors in Bladder Carcinoma. (Eng) Lynch, H. T. (Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE); Walzak, M. P.; Fried, R.; Domina, A. H.; Lynch, J. F. *J Urol* 122(4): 458-461; 1979.

Studies on two families showing an excess of carcinoma of the bladder are reported. Cancer was manifested in five generations of the first family: carcinoma of the breast occurred in the proband's paternal grandmother and paternal great-grandmother; transitional cell carcinoma of the bladder occurred in the proband at 52 yr of age; transitional cell carcinoma of the renal pelvis occurred at age 62 in the proband's paternal uncle; and the daughter of the proband died of neuroblastoma at age 4 yr. In the second family the proband's father had verified carcinoma of the colon and the proband and two siblings suffered from transitional cell carcinoma

of the bladder and/or renal pelvis. One of the siblings developed transitional cell carcinoma of the bladder at 24 yr of age and also had multiple sclerosis, as did one brother not affected by cancer. In neither family were there consistent occupational exposures, but there was an excess of cigarette smoking among at least some of the individuals affected by cancer. It is proposed that the etiology of familial bladder cancer may be complex, possibly involving other associated malignant neoplasms and/or certain non-neoplastic disorders in addition to specific carcinogen exposures. (21 refs)

- 79-7133 **Familial Ovarian Cancer.** (Eng) Lurain, J. R. (Dept. Gynecologic Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Piver, M. S. *Gynecol Oncol* 8(2): 185-192; 1979.

The occurrence of epithelial ovarian cancer in a mother, three of her five daughters, and one of her eight granddaughters is reported. Adenocarcinoma of the ovary was histologically confirmed in all but the mother as poorly differentiated papillary adenocarcinoma (2), poorly differentiated adenocarcinoma (1), and moderately differentiated endometrioid adenocarcinoma (1). Age at diagnosis was 33-51 yr (mean 42 yr). Three of the five women are alive 6, 5, and 2 yr after diagnosis, two without evidence of disease. All patients were parous, and there were no known predisposing disorders. This report brings to 27 the number of families recorded with multiple cases of epithelial ovarian cancer. In most cases, the age of onset of ovarian cancer is lower than in nonfamilial cases. The tumors do not appear to differ clinically or histologically from sporadically arising tumors. The prognosis in these families is generally unfavorable; of 92 women for which follow-up data is available, only 8 are now alive, 5 for <3 yr, 1 for 5 yr, 1 for 6 yr, and 1 for an unknown length of time. The pattern of familial occurrence suggests autosomal dominant inheritance. Prophylactic oophorectomy appears to be indicated in women in these ovarian cancer families, but it can probably be safely postponed until after the childbearing years. (27 refs)

- 79-7134 **Investigation of a Family Suspected of Being at High Risk for Cancer.** (Eng) Elwood, J. M. (Div. Epidemiology, Cancer Control Agency British Columbia, 700-686 West Broadway, Vancouver, BC V5Z 1G1, Canada); Crawford, G. M.; Werner, M. *Can Med Assoc J* 121(5): 559-563; 1979.

The family of a 46-yr-old woman with bilateral breast cancer was investigated as a suspected high-risk family for cancer. Interviews and review of hospital records and death certificates provided information for 199 family members, 19 of whom had cancer. In generation I, 1/3 women surviving infancy and 5/8 men died of cancer. In generation II, the patient's mother and aunt both had breast cancer. Among the 14 women in this generation, 5 had cancer (2 of the breast and 3 of the ovary); there was one cancer, a lymphoma, among the 15 men. The expected numbers were 1.24 and 1.16, respectively. The excess number in the women was statistically significant. In generation III, apart from the index patient, there was one woman with cervical cancer and two men with cancer. The excess was not significant. Only 1/83 members of the fourth generation had cancer, but most members were under 15 yr old. Although there was an increased incidence of cancer in the

women in the second generation, striking excesses were not seen in the next generation and there was no indication of a clear Mendelian pattern. (29 refs)

- 79-7135 **Tumor Phylloides of the Breast.** (Pol) Przysasz, T. (I. Klinika Chirurgiczna, Instytutu Chirurgii Centrum Kształcenia Podyplomowego WAM, ul. Szaserow 128, 00-909 Warsaw, Poland); Badowski, A. *Wiad Lek* 32(14): 971-975; 1979.

Tumor phylloides were diagnosed in four women in a series of 1,304 women operated for breast tumors during a 10-yr period. The four women were aged 37-51 yr (av 43.5 yr), and all had had at least one childbirth and had breastfed their babies. The tumor was unilateral in all cases, being located in the left breast or right breast in 2 cases each. The tumors were hard and fairly large (7-15 cm, av 11 cm). They showed a typical biphasic growth; the length of the first growth phase was 7-12 yr; that of the second phase, 4-24 mo. All four tumors developed from intracanalicular fibroadenomas. Malignant transformation or recurrence after excision was not seen. The findings are in agreement with data in the literature. (8 refs)

- 79-7136 **Noninvasive Precursor Lesions of Adenocarcinoma and Mixed Adenosquamous Carcinoma of the Cervix Uteri.** (Eng) Christopherson, W. M. (Dept. Pathology, Univ. Louisville Sch. Medicine, P.O. Box 35260, Louisville, KY 40232); Nealon, N.; Gray, L. A. *Cancer* 44(3): 975-983; 1979.

In an attempt to establish incidence rates for in situ carcinoma of the cervix in which adenocarcinoma was either the only or a major component, 4,350 cases of cervical carcinoma reported to a uterine tumor registry during 1953-1975 were reviewed. The records of all patients with the diagnosis of adenocarcinoma in situ (AIS) or of squamous carcinoma in situ (CIS) plus AIS were examined, and 16 patients from this group were identified as having noninvasive cervical carcinoma. Four cases of AIS with microinvasion were also diagnosed, two having pure AIS and two having AIS in combination with CIS. Nine of the 16 patients had the combined form, and 7 had AIS only. The incidence rates, calculated per 100,000 women aged 20 yr and older, were 36.9 for invasive squamous carcinoma of the cervix, 49.0 for CIS, 2.5 for invasive adenocarcinoma, and 0.21 for AIS. It is suggested that the greater frequency of squamous carcinoma of the cervix could be explained by the ubiquity of squamous metaplasia in the highly sensitive transformation zone of women of the childbearing age. The lower than expected incidence found for AIS or combined AIS-CIS may be partly explained by the location of these lesions in the endocervix, an area less accessible to cytologic detection. It is postulated that squamous cell carcinoma, adenocarcinoma, and mixed adenosquamous cell carcinoma of the uterine cervix all have a common cell origin in the subcolumnar reserve cell. (33 refs)

- 79-7137 **Development of Leydig Cell Tumors and Onset of Changes in the Reproductive and Endocrine Systems of Aging F344 Rats.** (Eng) Turek, F. W. (Dept. Biological

Sciences, Northwestern Univ., Evanston, IL 60201); Desjardins, C. *J Natl Cancer Inst* 63(4): 969-975; 1979.

Reproductive and endocrine system changes associated with the age-dependent onset of spontaneous testicular interstitial cell tumors were examined in male F344 rats. Histological examination of testes established that nodular interstitial cell hyperplasia was evident in three of five 12-mo-old rats and in all of five rats at 15, 18, 21, and 24 mo of age. Involution of the seminiferous epithelium was evident in all testes exhibiting extensive interstitial cell proliferation. Striking increments in serum prolactin and estradiol levels were noted with advancing age, whereas serum levels of follicle-stimulating hormone were unequivocally lower at 21 and 24 mo than at 6 mo of age. No measurable changes were detected in serum testosterone concentrations between 6 and 18 mo of age, but marked increments in this androgen, without any measurable change in circulating luteinizing hormone titers, were apparent in 21- and 24-mo-old rats. These findings point to a dynamic relationship between testicular interstitial cell tumorigenesis and age-related changes in the synthesis and/or secretion of gonadal and adenohipophyseal hormones. (35 refs)

See also:

- *(Rev.): 79-6604, 79-6607, 79-6611, 79-6615, 79-6622, 79-6629, 79-6632, 79-6636, 79-6637, 79-6638.
- *(Chem.): 79-6644, 79-6646, 79-6653, 79-6657, 79-6661, 79-6662, 79-6670, 79-6673, 79-6678, 79-6686, 79-6688, 79-6702, 79-6708, 79-6710, 79-6715, 79-6725, 79-6727, 79-6728, 79-6733, 79-6735, 79-6738, 79-6744, 79-6754, 79-6770, 79-6783, 79-6785, 79-6824, 79-6825, 79-6826, 79-6833, 79-6838, 79-6845, 79-6852, 79-6853, 79-6854, 79-6855, 79-6856, 79-6863, 79-6868.
- *(Phys.): 79-6875, 79-6885, 79-6894, 79-6896, 79-6899, 79-6901, 79-6902, 79-6905, 79-6910, 79-6911, 79-6913, 79-6917, 79-6918, 79-6919, 79-6920, 79-6925.
- *(Viral): 79-6929, 79-6967, 79-6974, 79-7002, 79-7010, 79-7012, 79-7030, 79-7062.
- *(Immun.): 79-7067, 79-7073, 79-7077, 79-7079, 79-7083, 79-7084, 79-7086, 79-7088, 79-7090.
- *(Epid.-Biom.): 79-7139, 79-7143, 79-7144, 79-7150, 79-7153, 79-7161, 79-7164, 79-7165, 79-7171, 79-7172, 79-7185.

- 79-7138 Lung Cancer Affecting Persons Under Forty. (Cze) Pesek, M. (Klinika tuberkulozy a respiracnych nemoci, LF KU, Sokolovska 52, 323 11 Plzen, Czechoslovakia); Houdek, J.; Simeckova, B. *Stud Pneumol Phtiseol Cech* 39(3/4): 200-203; 1979.

Lung cancer was diagnosed in a series of 2,100 patients (1,949 men and 151 women, male:female ratio 13:1) during a 22 yr period, and the 66 patients (51 men and 11 women, male:female ratio 5:1) aged under 40 yr were studied. Small-cell carcinoma was diagnosed in 21 men and 1 woman, epidermoid carcinoma in 21 men and 2 women, columnar-cell carcinoma in 11 men and 5 women, mixed tumor in 1 man, alveolar-cell carcinoma in 1 man and 1 woman, and polymorphocellular carcinoma in 4 men; the histological type was not established in 7 men and 2 women. Three men were under the age of 25 yr, 21 men and 2 women were in the age bracket 26-35 yr, and 27 men and 9 women were in the age bracket 36-40 yr. The distribution of the histological types in the women under 40 yr of age was similar to that found in all 151 women. Among the 51 men, 80.3% were smokers, whereas among the (11) women 72.7% were nonsmokers. The relationship between smoking and histological type is discussed. (13 refs)

- 79-7139 Hashimoto's Thyroiditis: A Possible Risk Factor for Lung Cancer Among Japanese Women. (Eng) Yamashita, N. (Dept. Neurophysiology, Inst. Brain Res., Faculty Medicine, Univ. Tokyo, Tokyo 113, Japan); Maruchi, N.; Mori, W. *Cancer Lett* 7(1): 9-13; 1979.

The association between Hashimoto's thyroiditis (HT) and malignancy was studied based on the Tokyo University Hospital autopsy reports of 1,896 women aged ≥ 20 yr. Of these patients, 29 had confirmed HT and 78 had probable HT. The number of breast cancers among the 107 confirmed and probable HT patients was 8, compared with 4.52 expected; the difference was not statistically significant. There were significantly more lung cancers (11 cases) in the HT group than expected (5.26 cases) ($p < 0.05$), but there was no inclination toward any particular histologic type of lung cancer in this group. Compared with the controls without HT, the HT patients with lung cancer showed no significant differences in cigarette smoking or history of radiation therapy. The findings suggest that HT and related changes could be one of the risk factors for lung cancer among Japanese women. (4 refs)

- 79-7140 History of Cervical Radiation and Incidence of Carcinoma of the Pharynx, Larynx, and Thyroid. (Eng) Sakamoto, A. (Dept. Pathology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Sakamoto, G.; Sugano, H. *Cancer* 44(2): 718-723; 1979.

The possible radiosensitivities of the pharynx, larynx, and thyroid for the induction of carcinoma were compared by analyzing 2,030 malignancies of one of these structures seen between 1947 and 1976. Most malignancies in the pharynx and larynx were squamous cell carcinomas, while adenocarcinoma was overwhelmingly

represented in the thyroid. There were 15 carcinomas in 14 patients (4 men, 10 women) with possible radiation-induced malignancies. All 14 patients had received x-ray therapy (1,300-20,000 rads, mean 6,600 rads) for benign neck lesions. Six cases of possible radiation-induced carcinoma occurred among 202 hypopharyngeal malignancies, while only 2 were observed among 1,208 in the larynx; 6 of 238 thyroid malignancies could have been radiation-induced. The hypopharynx and larynx were equally irradiated, but the difference in the frequency of radiation-induced carcinomas between these structures was statistically significant. The av interval between initiation of irradiation and onset of cancer was 28 yr. Possible radiation-induced carcinomas in the hypopharynx, larynx, and thyroid usually developed earlier than comparable naturally occurring carcinomas. It is concluded that the hypopharynx should be included in the high-risk group of human structures for cancer occurrence after irradiation. (16 refs)

- 79-7141 Interaction of Factors Associated with Cancer of the Nasopharynx. (Eng) Lin, T. M. (Dept. Public Health, Natl. Taiwan Univ., Coll. Medicine, #1 Sec. 1, Jin-Ai Rd., Taipei, Taiwan); Yang, C. S.; Tu, S. M.; Chen, C. J.; Kuo, K. C.; Hirayama, T. *Cancer* 44(4): 1419-1423; 1979.

The interaction of factors that have been associated with nasopharyngeal carcinoma (NPC) was studied retrospectively in 351 NPC patients. These factors include smoking, working in poorly ventilated areas (WPV), use of nasal balms or oil for nasal and throat problems (NBO), use of herbal drugs (HD), and high anti-Epstein-Barr virus (EBV) antibody titers. In general, the risk of NPC increased with the level of exposure to each of these factors. There appeared to be a synergistic association between smoking and each of the other factors, especially HD or WPV. Other synergistic interactions were seen between WPV and all other factors, between HD and increased anti-EBV antibody titer, and between NBO and HB plus increased anti-EBV antibody titer. (17 refs)

- 79-7142 Lymphomas in Renal Transplant Recipients: A Search for Clustering. (Eng) Kinlen, L. J. (Environmental Epidemiology Branch, Natl. Cancer Inst., Bethesda, MD 20205); Hoover, R. N. *Br J Cancer* 40(5): 790-802; 1979.

The registry of the American College of Surgeons was examined for evidence of space and time clustering of lymphomas among renal transplant recipients. Of the 16,869 patients treated at 283 transplant centers, 54, from 39 centers, developed lymphoid tumors. The overall incidence of lymphomas was 1.3/1,000/yr. Centers at which one transplant patient developed lymphoma subsequently showed an even higher subsequent rate (1.89/1,000). Although these differences were statistically significant, they suggested the possible involvement of a transmissible agent in the etiology of lymphoma. However, there was no evidence of space-time clustering or of a higher incidence in transplant patients who could have had direct contact with lymphoma patients in the in-

duction period; this suggests that the above findings were not due to the effects of a transmissible agent. (3 refs)

- 79-7143 Histopathological Changes of the Nasal Mucosa in Active and Retired Nickel Workers. (Eng) Torjussen, W. (Central County Hosp., Kristiansand, Norway); Solberg, L. A.; Hogetveit, A. C. *Br J Cancer* 40(4): 568-580; 1979.

Nasal biopsy specimens from the middle turbinate in 318 active and 15 retired nickel workers and in 57 controls were examined histologically to study the prevalence of nasal carcinoma or possible precancerous mucosal changes in nickel-exposed individuals. The histopathological changes were evaluated according to a point-score scale, and the results were correlated with age, smoking habits, duration and type of nickel exposure, and nickel concentrations in nasal mucosa, plasma and urine. The explanatory values of these factors on the histopathology were estimated by stepwise multiple regression analysis. Two nickel workers from the roasting/smeltering department (0.6%), both employed 28 yr at the plant, had nasal carcinoma; and carcinoma in situ was found in one of these cases. Epithelial dysplasia was found in about 12% of active and 47% of retired nickel workers. One of the controls, a male carpenter, had dysplasia. These histopathological changes may be precancerous lesions, as they are almost exclusively found in active and retired nickel workers with enhanced risk of nasal carcinoma. Loss of respiratory epithelium and development of squamous epithelium were regarded as nonspecific histopathological changes. These changes were seen in all groups, although the incidence was significantly higher in the nickel-exposed groups. Duration of nickel exposure, type of nickel-refining work, and tobacco consumption were the independent variables that, taken together, had the highest explanatory values for the histopathological changes. (26 refs)

- 79-7144 Histopathologic Changes of Nasal Mucosa in Nickel Workers. A Pilot Study. (Eng) Torjussen, W. (Central County Hosp., 4601 Kristiansand S, Norway); Solberg, L. A.; Hogetveit, A. C. *Cancer* 44(3): 963-974; 1979.

Histologic examination of standard biopsy specimens from nasal mucosa were performed on 98 former and present employees at a nickel refinery and on 61 controls. Histologic characteristics of the epithelium were graded blindly according to a point score table. The histologic scores were compared to certain epidemiologic data, such as the degree and duration of nickel exposure, duration of industrial work without nickel exposure, age, and smoking habits. High histologic scores were correlated to high nickel exposure, to the duration of this exposure, to age, and to industrial work not involved with nickel. One person with nasal carcinoma was detected in the nickel-exposed group. During the investigation period, three additional nasal carcinomas in former nickel workers were discovered and later included in the study. Furthermore, 18 cases of epithelial dysplasia were found in the nickel-exposed group, whereas none were found among controls. The subjects with nasal carcinomas were or had been working with processes that gave an estimated high nickel dust exposure. All the individuals with epithelial dysplasia were nickel process workers. (32 refs)

Hosp., Kristiansand S, Norway). *Acta Otolaryngol (Stockh)* 88(3/4): 279-288; 1979.

Rhinoscopy and x-ray examination were performed on 318 nickel workers and 57 controls to study the usefulness of these methods in detecting cancerous and precancerous mucosal changes. The clinical and radiological findings were compared with histopathological data and mucosal nickel concentrations determined in nasal biopsy material from the middle turbinate, with duration of nickel exposure, and with tobacco smoking habits. The nickel-exposed subjects had a statistically significant increase in pathological changes over the controls (43% vs 26%, $0.01 < p < 0.02$), mainly due to differences in the frequency of hyperplastic rhinitis. Thirteen nickel workers (4%) had nasal polyps. Two of these cases, both employed at the nickel refinery for 28 yr, appeared to have nasal carcinoma revealed by histological examination. No distinct association was established between rhinoscopic findings and epithelial dysplasia found by histological examination. The explanatory values for the rhinoscopic findings of different factors, such as working category, age, duration of nickel exposure, grams tobacco smoked per week, and nickel content of nasal mucosa, were evaluated by applying a stepwise multiple regression analysis. Number of years from first employment at the nickel refinery and tobacco consumption were the only explanatory factors that showed a statistically significant correlation to the rhinoscopic findings. The radiological examination revealed few characteristic findings. Chemical analysis of cigarettes handrolled by nickel workers showed high nickel concentrations compared with uncontaminated cigarettes. (13 refs)

- 79-7146 Malignant Neoplasms in Saudi Arabia. (Eng) Stirling, G. (Pathology Dept., Coll. Medicine and Allied Sciences, P.O. Box 1540, Jeddah, Saudi Arabia); Khalil, A. M.; Nada, G. N.; Saad, A. A.; Raheem, M. A. *Cancer* 44(4): 1543-1548; 1979.

A series of 1,000 consecutive malignant neoplasms diagnosed over a 3-yr period in Saudis living in the Western Region of Saudi Arabia was analyzed. The most common malignancy was skin cancer (155 patients), with squamous cell carcinoma being most prevalent (73). This was followed by malignant lymphoma (128 patients), of which Hodgkin's disease was the most common (56) and showed a male predominance (1.9:1.0). The peak age for Hodgkin's disease was the second decade, compared with the third decade in Western countries. The proportions of the subtypes of Hodgkin's disease were also different from those encountered in many other countries, in that there was a greater proportion of the mixed cellularity type (60.7%) and a lower proportion (8.9%) of the nodular sclerosis type. Eighteen of the 39 patients with reticulum cell/poorly differentiated lymphomas presented with primary abdominal malignancies, and six of these patients were girls (7 mo-11 yr old). The mouth, including the tongue, was the most common site for gastrointestinal system cancer (81 patients), followed by the esophagus (59 patients). The colon and rectum accounted for 40 cancer cases. Only 40 cases of lung cancer were diagnosed during this period. Breast cancer (74 cases) was the most common malignant neoplasm among women. Cervical carcinoma was the most common female genital tract malignancy (42 patients), followed by cancer of the uterus (24 cases) and ovary (21 cases). There were 52 soft tissue sarcomas. No malignant neoplasms of the CNS were detected. (16 refs)

- 79-7145 Rhinoscopic Findings in Nickel Workers, with Special Emphasis on the Influence of Nickel Exposure and Smoking Habits. (Eng) Torjussen, W. (Central County

- 79-7147 Trophoblastic Tumors in Greenland. (Eng) Nielsen, N. H. (Dept. Pathology, Rigshospitalet, Copenhagen,

Denmark); Hansen, J. P. *J Cancer Res Clin Oncol* 95(2): 177-186; 1979.

The incidences of hydatidiform mole, invasive mole, and choriocarcinoma in female natives of Greenland during the period 1950-1974 were studied. During this period, 37 cases of hydatidiform mole not followed by malignancy and 11 cases of invasive, trophoblastic tumors (IGTT) occurred among the women studied. The overall incidence of benign mole was 1:850 births, only slightly higher than most incidences in low-risk areas like Western Europe, North America, Australia, and Israel. In contrast, the overall incidence of IGTT, 1:2,861 births, and the minimum incidence of histologically confirmed choriocarcinoma, 1:5,245 births, are among the highest population-based incidences on record. A marked increase in incidence of both hydatidiform mole and IGTT was found late in reproductive life. A recent high incidence of mole among teenagers increased the incidence with statistical significance during the last 10 yr of the study, whereas max incidence of IGTT was found between 1960 and 1964. A strong association existed between hydatidiform mole and IGTT. During the study period, Greenlandic women with hydatidiform moles had a 20% risk of developing IGTT, and 64% of IGTT cases were preceded by pregnancy during which a mole was found. Four cases of benign mole, but no case of IGTT, occurred among the small group of Danish women living in Greenland. The incidence, 1 mole/685 births, was higher than among the indigenous population, although the latter had a lower socioeconomic status. The reason for the high incidence of IGTT among indigenous Greenlanders remains unknown. The predominant HL-A 9 antigen could reflect genetic predisposition. (49 refs)

- 79-7148 Variation of Melanoma Incidence with Latitude in North America and Europe. (Eng) Crombie, I. K. (Dept. Social Medicine, Univ. Birmingham, Birmingham, England). *Br J Cancer* 40(5): 775-782; 1979.

The relationship between melanoma incidence and latitude was investigated among North American and European Caucasians. Data collected by 43 population-based cancer registries was used. In North America, melanoma incidence increased with decreasing latitude, supporting the role of UV light in the induction of melanoma. Within England, data from the National Cancer Registration scheme also showed the trend of increased frequency of melanoma with decreasing latitude. In contrast, the trend across Europe was in the opposite direction, of increasing melanoma incidence with increasing latitude. It is suggested that across Europe, there is a range of skin color from dark in the south to light in the north, which gives rise to a range of susceptibility to the induction of melanoma by UV. The effect of this susceptibility must be large enough to overwhelm the opposing effect of decreased UV intensity at higher latitudes, and this emphasizes the dangers of excessive solar exposure to fair-skinned individuals. The population of England may be a sufficiently random mix of skin color, owing to repeated invasions, for the effect of UV intensity to be observed. (15 refs)

- 79-7149 Plasma IgA, IgG and IgM and Their Relationship to Breast Cancer in British, Japanese and Hawaiian-Japanese Women. (Eng) Wang, D. Y. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Goodwin, P. R.; Bulbrook, R. D.; Hayward, J. L.; Abe, O.; Utsumiya, J.; Kumaoka, S.; Greenwood, F. C.; Glober, G.; Stemmerman, G. *Cancer* 44(2): 492-494; 1979.

IgA, IgG, and IgM levels were measured in 44 normal Hawaiian-Japanese women, 35 British women, and 37 Japanese women living in Tokyo, none of whom had been taking steroidal contraceptives for ≥ 1 yr. The Hawaiian Japanese women had the same levels of IgA as Japanese women, the same levels of IgM as British women, and were intermediate for IgG levels. The mean level of IgM in 28 Japanese patients with breast cancer was similar to that in normal British or Hawaiian-Japanese women and significantly lower than that in normal Japanese women ($p < 0.01$). The finding that Hawaiian-Japanese women with an increased risk of breast cancer, compared with indigenous Japanese, have an IgM level similar to British women and Japanese patients with breast cancer supports the hypothesis that differences in IgM levels reflect alterations in humoral immunity and that these differences are associated with racial differences in breast cancer incidence. (10 refs)

- 79-7150 Plasma and Urinary Androgens in Women with Varying Degrees of Risk of Breast Cancer. (Eng) Wang, D. Y. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Moore, J. W.; Thomas, B. S.; Bulbrook, R. D.; Hoare, S. A.; Tong, D.; Hayward, J. L. *Eur J Cancer* 15(10): 1269-1274; 1979.

Plasma levels of dehydroepiandrosterone (DHE), DHE sulfate Δ^4 -androstenedione, and Δ^5 -androstenediol were determined in 386 healthy women (30-69 yr of age) assigned to four groups with mean calculated risk of breast cancer (estimated from the age of menarche, age at first child, family history, and amount of etiocholanone in the urine) of 0.016, 0.023, 0.051, or 0.111, respectively. Plasma DHE sulfate and Δ^5 -androstenediol levels in the group with highest estimated risk were significantly lower than in the other three groups; however, there were no significant differences among postmenopausal women. No correlation between estimated cancer risk and levels of DHE Δ^4 -androstenedione was observed. (13 refs)

- 79-7151 Cancer Register in Greenland. (Dan) Boggild, J. (Landslaegeembedet, Copenhagen, Denmark); Clemmesen, J.; Hart Hansen, J. P.; Nielsen, N. H. *Ugeskr Laeger* 141(28): 1946-1947; 1979.

Epidemiological data on cancer in Greenland are presented. Very high incidences of cancer of the uterine cervix, rhinopharynx, salivary glands, and esophagus have been reported. Between 1970 and 1974, the age-adjusted incidence of cancer of the uterine cervix was 84.8/100,000, which is more than 2.5 times higher than the incidence in Denmark during the same period. The incidence has risen considerably compared with that during the preceding 15 yr. The age-adjusted incidence of rhinopharyngeal cancer between 1965 and 1976 was 12.3 in men and 8.5 in women, which is slightly lower than the highest incidence rates in China. Most salivary gland tumors found in Greenland are anaplastic carcinomas with lymphocyte infiltration. As the salivary gland tumor tissue is histologically identical with the rhinopharyngeal cancer, many may be metastases. Statistically significant cumulation of esophageal cancer was found in the three southernmost districts of Greenland. Between 1965 and 1974, the incidence in both men and women was five times higher than in the rest of Greenland. The ecological conditions in southern Greenland may play a role in this high incidence of esophageal cancer. (4 refs)

- 79-7152 Incidence of Myeloid Leukaemia in Lancashire. (Eng) Geary, C. G. (Dept. Clinical Hematology, Univ. Man-

chester, Manchester, England); Benn, R. T.; Leck, I. *Lancet* 2(8142): 549-551; 1979.

The identification of a cluster of cases of acute and chronic myeloid leukemia in a single general practice in Lancashire prompted a formal analysis of the incidence of these diseases in most of Lancashire, based on data collected by the Regional Cancer Registry in Manchester during a 12-yr period. The number of registered cases of myeloid leukemia was determined and converted to a standardized registration ratio. The analysis revealed a doubling in the standardized registration ratio for myeloid leukemia in Lancashire as a whole between 1965-1970 and 1971-1976. The localities into which Lancashire was divided for this analysis did not differ significantly from one another in the increases observed. The increased incidence of leukemia in this area represents a substantially larger increase than that which has occurred nationally in the same period and is unlikely to be due solely to more accurate diagnosis or reporting. Although no chemical leukemogen was identified, it is possible that a proportion of the cases are due to extrinsic or intrinsic leukemogens, acting in susceptible individuals. (13 refs)

- 79-7153 Axillary Forms of Hodgkin's Disease. Considerations on Etiology and Clinical Characteristics. (Ger) Weh, H. J. (Institut de Recherches sur les Leucémies et les Maladies du Sang, U.E.R. d'Hématologie, Hôpital Saint-Louis, 2, place du Docteur Fournier, F-75475 Paris Cedex 10, France); Andrieu, J. M. *Med Welt* 30(40): 1460-1462; 1979.

A possible correlation between the rare axillary localization of Hodgkin's disease (HD) with injury and infection of the hands or arms was studied in 16 HD patients. The patients had Stage I HD localized to one axillary region only (LAR). The av age at diagnosis was 40.9 yr, compared with an av of 28.9 yr among 447 HD patients with usual localizations. The group with LAR-HD contained only 3 women; this sex distribution is different ($p < 0.001$) from the men:women ratio of 1.3 in the usual HD group. Only 4/16 LAR patients reported no manual labor in their work history, and 3 of these reported frequent injury or irritation of the arms or axilla (eg, shaving injury). The remaining 12 patients reported at least 10 yr of manual labor that resulted in frequent hand and arm injuries. Manual labor is the main occupation of 35% of the French population, from which the LAR group was drawn. Two of the LAR group had lymphocyte-rich HD, 9 had nodular sclerosing HD, 4 had mixed-cellular HD, and 1 had lymphocyte-poor HD. Fourteen of these patients are in full remission, with an av survival time of 41 mo, and two died at 69 and 75 mo. Isolated localization of HD to the axilla has been found in 2.5%-5.7% of HD cases in different series. The LAR group described differs from the usual HD group in the higher age of diagnosis and the preponderance of men and manual laborers. Frequent injury of the hands or arms may provide an entrance for an agent causing HD in susceptible individuals. (25 refs)

- 79-7154 Occupational Handling of Chemicals Preceding Hodgkin's Disease in Men. (Eng) Olsson, H. (Dept. Oncology, Univ. Hosp., S-221 85 Lund, Sweden); Brandt, L. *Br Med J* 2(6190): 580-581; 1979.

The case records of 88 men treated for Hodgkin's disease at a Swedish hospital during 1973-1978 were examined for a possible relationship between Hodgkin's disease and occupations involving the handling of chemicals. Seventeen men had occupations in-

dicating that they handled chemicals (chemists, 2; painters and sprayers, 5; glass and pottery workers, 5; rubber product workers, 2; and 1 each chemical processing, plastics, and photographic laboratory workers). In three control groups (two consisting of persons without cancer and one of 32 men with chronic leukemias), 2/100, 3/100, and 1/32 individuals, respectively, had occupations involving chemical handling. The differences between the group with Hodgkin's disease and each of the control groups were significant. Only 2/35 patients with Hodgkin's disease aged 20-30 yr were occupationally exposed to chemicals compared with 8/31 of those aged 31-50 yr and 7/22 of those over 50-65 yr old. This may indicate that occupational exposure to chemical oncogenic agents may be important in Hodgkin's disease in men over 30 yr old while other etiological factors may be more important in the younger age groups. The results also suggest that an effort should be made to define environmental hazards that may be important in the development of Hodgkin's disease. (3 refs)

- 79-7155 The Chemotherapy of Plasma-Cell Myeloma and the Incidence of Acute Leukemia. (Eng) Bergsagel, D. E. (NCIC Epidemiology Unit, Faculty Medicine, Univ. Toronto Hosp., McMurrich Building, Toronto, Ontario M5S 1A8, Canada); Bailey, A. J.; Langley, G. R.; MacDonald, R. N.; White, D. F.; Miller, A. B. *N Engl J Med* 301(14): 743-748; 1979.

Previously untreated myeloma patients (196 men, 168 women) were randomly assigned to one of three treatment groups: Group A, melphalan and prednisone followed by either cyclophosphamide or carmustine if relapse or progression occurred (125 patients); Group B, melphalan, cyclophosphamide, carmustine, and prednisone on an alternating schedule (123 patients); and Group C, the same four drugs on a concurrent schedule (116 patients). The composition of the three groups was similar with respect to age, sex and M-protein types, and various prognostic factors (performance status, clinical stage, and the initial blood urea nitrogen). There were no significant differences in response rate or survival among the three groups. It was not possible to identify a subgroup that responded better to the combination of alkylating agents than to melphalan and prednisone alone. The survival of patients producing only λ chains was shorter than expected. Acute leukemia developed in 14 patients, and ring sideroblasts, a presumed preleukemic change, were reported in an additional 18 patients. There was no significant difference in the incidence of leukemia among the three groups. The observed incidence of acute leukemia was much greater than expected for all the groups. It is concluded that the combination of the four drugs is no better than melphalan and prednisone for inducing responses or prolonging the survival of myeloma patients. (25 refs)

- 79-7156 Case-Control Study of Hair Dye Use by Patients with Breast Cancer and Endometrial Cancer. (Eng) Stavray, K. M. (Ontario Cancer Treatment Res. Foundation, Dept. Epidemiology, Univ. Western Ontario, London, Ontario N6A 5B7, Canada); Clarke, E. A.; Donner, A. *J Natl Cancer Inst* 63(4): 941-945; 1979.

A case-control study of permanent and semipermanent hair dye use by women with breast or endometrial cancer was carried out. The patients included 50 breast cancer patients in London, Ontario, 35 breast cancer patients in Toronto, and 36 patients with endometrial cancer in Toronto. In London, controls consisted of hospitalized women with diseases other than cancer; in Toronto, controls were selected from women living in the same

neighborhood as the cancer patients. The results did not suggest an increased risk of either breast or endometrial cancer in users of permanent or permanent and semipermanent dyes combined. Although the numbers of cases and controls were small, the consistency of the results for both sites, in both study centers, and the absence of any clear positive relationship between various measures of intensity of use and cancer risk provided evidence that a large increase in risk was not missed. (21 refs)

- 79-7157 Breast Cancer in Black American Women. (Eng) Austin, H. (Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Avenue, Boston, MA 02115); Cole, P.; Wynder, E. *Int J Cancer* 24(5): 541-544; 1979.

Results of a case-control study of breast cancer among Black American women conducted in seven hospitals in New York city from 1969 to 1975 are reported for 127 cases and 317 controls. Compared to women with a first birth before age 19 yr, those with a first birth after 25 yr of age had a relative incidence rate for breast cancer of 3.8 and 2.2 for the pre- and postmenopausal age-groups, respectively. Compared to nulliparous women, parous women had a relative incidence rate of 0.6 and 0.7 for pre- and postmenopausal women, respectively. The incidence rate for women reaching menopause after age 49 yr was estimated to be 3.1 times that of women with a menopause before 45 yr of age. Thus, the known risk factors for breast cancer among Whites also appear to apply to Blacks. The incidence rate of breast cancer has increased among younger Blacks since 1947 and is now similar to that of younger Whites, while among older women the incidence rate is still appreciably higher for Whites. This pattern could be explained by common exposures to etiological agents (eg, dietary or environmental factors) among women of both races born since about 1925. (14 refs)

- 79-7158 Cancer and Scleroderma. (Eng) Duncan, S. C. (Dept. Dermatology, Mayo Clinic, Mayo Foundation, Rochester, MN); Winkelmann, R. K. *Arch Dermatol* 115(8): 950-955; 1979.

Experience with patients who had both scleroderma and an internal malignancy is presented. Of 2,141 scleroderma patients seen at the Mayo Clinic between 1959 and 1975, 78 had 87 internal malignancies. The relative frequency of the types of cancers was similar to that for the general population. The increased numbers of patients with breast and uterine carcinomas were consistent with the female preponderance in scleroderma. Contrary to previous reports, lung carcinoma was not the most frequent malignancy associated with scleroderma. Breast carcinoma was the most frequent malignancy (18 cases), followed by lymphoma-leukemia malignancies (11 cases). Both conditions developed within a 3-yr period in 45/66 patients with systemic scleroderma, and this subgroup comprised a high mortality group. (44 refs)

- 79-7159 Mathematical Models and the Statistical Analyses of Cell Transformation Experiments. (Eng) Gart, J. J. (Biometry Branch, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20205); DiPaolo, J. A.; Donovan, P. J. *Cancer Res* 39(12): 5069-5075; 1979.

Statistical methods are developed and applied to the fitting of the one-hit curves to chemically induced transformations in Syrian

hamster colonies. Data from several experiments in two laboratories are shown to fit the model well for benzo(a)pyrene at all but the highest doses. The ratio of the estimated parameters of the one-hit curves ("transformicities") is proposed as a measure of the enhancement by x-irradiation. Statistical tests for possible nonrandom variation among dishes are developed for use when a sample of dishes is used to estimate the total number of surviving cells. The methods of fitting and estimation are also extended to this case. Further analyses exclude selection as an explanation for the observed increase in transformation frequency with increased carcinogen concentration. The reproducibility of the fit of the one-hit model and the radiation enhancement measures is attributed to the uniqueness of this in vitro system in which the direct target cell-insult interaction is not modulated by host intervention. (16 refs)

- 79-7160 Risk Factors for Nodular Sclerosis and Other Types of Hodgkin's Disease. (Eng) Henderson, B. E. (Dept. Community and Family Medicine, Univ. Southern California Sch. Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033); Dworsky, R.; Pike, M. C.; Baptista, J.; Menck, H.; Preston-Martin, S.; Mack, T. *Cancer Res* 39(11): 4507-4511; 1979.

The age-adjusted incidence rates of nodular sclerosis in Los Angeles County from 1972-1975 were 58% lower in Mexican-Americans and 42% lower in blacks than in non-Mexican whites. In the latter group, rates were the same for each sex, with the curve of age-specific incidence peaking in young adulthood. The incidence of nodular sclerosis was directly associated with social class. In contrast, the rates for other histological varieties of Hodgkin's disease (lymphocyte predominance, mixed cellularity, lymphocyte depletion) were 12% lower in Mexican-Americans and 34% lower in blacks. In non-Mexican whites, the rates were 92% higher in men and increased gradually with age; there were no clear trends with social class. These characteristics support the hypothesis that, at least for purposes of etiology, the nodular sclerosis form of this disease should be considered a distinct entity. Self-administered questionnaires were completed by 218 of the 1972-1973 Hodgkin's disease patients and 218 individually matched neighborhood controls. Significantly high risk ratios for Hodgkin's disease were found for prior appendectomy (risk ratios = 1.9, $p = 0.01$) and for past amphetamine use (risk ratios = 3.0, $p = 0.01$). The elevated risk associated with amphetamine use had been found in a previous study. (22 refs)

- 79-7161 Hodgkin's Disease in Childhood. (Eng) Alsabti, E. A. (7511 Teall Run, Houston, TX 77071). *J Cancer Res Clin Oncol* 95(1): 75-81; 1979.

The relationship of histologic type to age, sex, and survival was studied among 103 children with Hodgkin's disease (HD) in Iraq. The children ranged in age from 1.5-16 yr, and the male:female ratio was 3.1:1. Subtype distribution did not vary significantly with sex. Of the 103 cases, 16 showed lymphocytic predominance (LP), 13 showed lymphocytic depletion (LD), 13 were classified as nodular sclerosis (NS), and 62 showed mixed cellularity (MC). Mediastinal masses were observed in 7/13 NS cases; the predominant location in other subtypes was the cervical lesion. Metastasis was found in four patients with the MC subtype and one with LP. Lymph node biopsies of three patients, all of whom were from rural areas, showed granulomatous inflammation in association with HD; two of these patients had a family history of tuberculosis. Survival during the first year after diagnosis was significantly higher among NS patients (96%) than among MC pa-

tients (72%) ($P < 0.005$). None of the patients with LD subtype survived beyond the first year. The 3-yr survival rates were similar among patients with NS and LP subtypes. (34 refs)

79-7162 Acquaintance Networks Among Leukemia and Lymphoma Patients. (Eng) Greenwald, P. (Div. Epidemiology, New York State Dept. Health, Tower Bldg., Empire State Plaza, Albany, NY 12237); Rose, J. S.; Daitch, P. B. *Am J Epidemiol* 110(2): 162-177; 1979.

A quantitative epidemiologic method that utilizes detailed social interaction data was developed to determine if acquaintanceship patterns among leukemia and lymphoma patients differ from those among healthy people. A case-control study of clustering through acquaintanceship among 20 lymphoma and 17 leukemia patients was conducted for the years 1967 through 1972 in Orleans County, New York. Data on acquaintanceship linkage were gathered from the source cases and controls, and from their acquaintances yielding a data base of 13,409 unique individuals linked by acquaintances. Three different analyses were carried out: a statistical analysis of linkage via intermediaries of case pairs in comparison with control pairs; a computer simulation of disease transmission from selected source cases to selected targets and controls based on the acquaintance data; and a secondary attack rate type analysis. The first two types of analysis yielded statistically significant case-control differences at the .05 level. The third method also yielded a positive result but was not subject to quantitative hypothesis testing. These epidemiologic methods for disease with long induction periods merit further study. (33 refs)

79-7163 Comparison of Virus-positive and Virus-negative Cases of Feline Leukemia and Lymphoma. (Eng) Francis, D. P. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA 02115); Cotter, S. M.; Hardy, W. D.; Essex, M. *Cancer Res* 39(10): 3866-3870; 1979.

The clinicopathological and epidemiological aspects of 184 cases of feline leukemia and lymphoma diagnosed in Boston between 1972 and 1976 were investigated. Fifty-eight percent of cases were lymphoma, and 42% were leukemia. Sixty-seven percent of the cats had positive fluorescent antibody tests for circulating feline leukemia virus. The rest (33%) were virus-negative. The virus-positive and virus-negative cases were remarkably similar, except for their age at diagnosis. Virus-negative cats tended to be older (mean age at diagnosis, 4.9 yr) compared with virus-positive cats (3.5 yr). Among the 22 cats in which leukemia or lymphoma was diagnosed after the age of 8 yr, 15 were virus-negative. The minimum mean induction period (time from first positive virus test to diagnosis of cancer) for 19 cats that were virus-positive and healthy at their first test was 16.7 mo (range, 2-41 mo). (30 refs)

79-7164 Idiopathic Refractory Sideroblastic Anemia: Incidence and Risk Factors for Leukemic Transformation. (Eng) Cheng, D. S. (Dept. Internal Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT 84132); Kushner, J. P.; Wintrobe, M. M. *Cancer* 44(2): 724-731; 1979.

The clinical course of 29 patients (19 men, 10 women; aged 19-88 yr) with idiopathic refractory sideroblastic anemia (IRSA) is reported. Four patients died with acute leukemia an av of 6.8 yr after the onset of the anemia. A literature review revealed that

31/297 patients with IRSA developed acute leukemia. Of the 31 cases, 9 were reported in detail; the characteristics of these 9 patients and the 4 reported in this study with IRSA terminating in acute leukemia were compared with those of the 25 patients in the present series who did not develop leukemia. The risk factors for leukemic transformation include a more severe anemia at presentation, a lower reticulocyte count, an increased transfusion requirement, and thrombocytopenia. There was a male preponderance of 10:3 in the leukemic group, compared with the overall male:female ratio of 2:1 in patients with IRSA. A low leukocyte alkaline phosphatase (LAP) score also appeared to be associated with leukemic transformation. (57 refs)

79-7165 Cancer in a Community Subject to Air Pollution by Solvent Vapors. (Eng) Capurro, P. U. (P.O. Box 218, Elkton, MD 21921). *Clin Toxicol* 14(3): 285-294; 1979.

A population of 117 people exposed for >5 yr to solvent vapors from a chemical plant were followed for 6 yr, October 1968 through September 1974. Solvent vapors detected in the study were: methyl ethyl ketone, methyl isobutyl ketone, acetone, methanol, isopropyl alcohol, butanol, amyl alcohol, isoamyl alcohol, benzene, toluene, xylene, phenol, nitrophenol, nitrochlorobenzene, chlorobenzene, ethyl acetate, ethyl ether, furan, tetrahydrofuran, methylchloride, methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, tichloroethane, acrylonitrile, and formaldehyde. During this period there were 14 deaths, 7 due to malignancy, compared to an expected 6 deaths, one of which would be from cancer. Lymphomas were definitely increased (4 in 6 yr); these 4 people also worked at one time in a paper mill which preceded the chemical plant in the same location. The ratio of observed to expected lymphoma deaths was 3/9.0187 or 160-fold. All of the people who developed lymphomas were diagnosed ≥ 4 yr after the initial exposure to solvents. Other cancers diagnosed in this group of 23 cases include cancer of the pancreas and larynx, Hodgkin's disease, leukemia, and reticulum cell sarcoma. (11 refs)

79-7166 Anaplastic Carcinoma of the Thyroid in a Population Irradiated for Hodgkin's Disease, 1910-1960. (Eng) Getaz, E. P. (322 E. Center St., West Bridgewater, MA 02379); Shimaoka, K. *J Surg Oncol* 12(2): 181-189; 1979.

The incidence of anaplastic carcinoma of the thyroid (ACT) was studied in 520 patients treated for Hodgkin's disease during the period 1910-1960. Of the 520 patients, 328 were male, 192 were female; 505 were white, and 15 were black. The mean age was 38.6 yr (range, 1.75-80 yr). Of the 494 patients who had been irradiated, 439 had been irradiated in the cervical and/or mediastinal areas. The mean survival time was 4.21 yr and was 6 mo longer for female patients than for male patients. The mean survival of the irradiated group was 4.95 yr. Of the 141 patients who survived ≥ 5 yr, 2 developed anaplastic carcinoma (1.42%). These two patients were among only six who survived >30 yr (33.3%). The incidence of ACT in Hodgkin's disease is far higher than would be expected in the population at large (0.8/100,000). It is possible that patients receiving a high dose of radiation to the cervical region, particularly when bipedal lymphangiography has been carried out, should remain on long-term thyroid suppressive therapy. (55 refs)

79-7167 Anatomic Distribution of Malignant Melanoma of the Skin Among Non-Caucasians in Hawaii. (Eng) Hinds,

M. W. (Epidemiology Program, Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI). *Br J Cancer* 40(3): 497-499; 1979.

The anatomical distribution of malignant melanoma among 64 non-Caucasian patients (Japanese, Hawaiian/part-Hawaiian, Filipino, and Chinese) in Hawaii during 1960-1977 is reported. Among men, the most common site was the feet (17/41), followed by the trunk (8), upper extremities (8), and head and neck (7). Among women, the head and neck was the most common site (6/23), followed by the lower extremities (5) and the feet (5). Thus, malignant melanoma is common on the feet of Hawaiian non-Caucasians, a pattern similar to that seen in blacks. The use of open-toed shoes and sandals is very common in Hawaii, lending support to the theory that trauma to the skin of the feet may be a predisposing factor in malignant melanoma of the feet. (9 refs)

79-7168 Skin Cancer Epidemiology: Research Needs. (Eng) Scotto, J. (Demography Section, Biometry Branch, NCI, NIH, Public Health Service Dept. Health, Education, Welfare, Bethesda, MD 20014); Fears, T. R. *Natl Cancer Inst Monogr* (50): 169-177; 1978.

An epidemiological study of skin cancer by the Environmental Protection Agency and the NCI now in progress is reviewed, and a detailed protocol of the study is provided. Past epidemiological data concerning carcinogenic UV rays (UV-B) and nonmelanoma skin cancer are too sparse and lack certain details such as exposure patterns and skin types, and the geographical area has been too narrow to allow for more precise measurement of the effects of stratospheric ozone depletion. The present relationships could change drastically with the addition of a few more points (geographical locations) and location-specific and demographic factors need to be evaluated. A special skin cancer study from June 1, 1977 to May 31, 1978 being conducted by NCI and the Environmental Protection Agency is aimed at determining the incidence of nonmelanoma skin cancer (basal and squamous cell carcinomas) in various population groups within the United States, and ascertaining and measuring the epidemiological factors that may contribute toward excess risk of nonmelanoma skin cancer in specific population groups. This study involves nine active areas within the contiguous United States, including a population of >20 million. The incidence and the interview compose this study: the basic incidence or morbidity survey is modeled after the earlier Third National Cancer Survey; the interview involves abstracts from medical records and a telephone interview questionnaire. The interview phase will provide the epidemiological data necessary to evaluate the degree of morbidity that may be related to high-risk factors. Samples of the physician's skin cancer record, the skin cancer abstract record, and the telephone questionnaire are provided. (13 refs)

79-7169 Reduced Prevalence of the Lucke Renal Adenocarcinoma in Populations of *Rana pipiens* in Minnesota. (Eng) McKinnell, R. G. (Dept. Genetics and Cell Biology, Univ. Minnesota, St. Paul, MN 55108); Gorham, E.; Martin, F. B.; Schaad, J. W. *J Natl Cancer Inst* 63(3): 821-824; 1979.

Northern leopard frogs (*Rana pipiens*) afflicted with the Lucke renal adenocarcinoma virtually disappeared from Minnesota in the autumn of 1977. Frogs from four sites in Minnesota counties with a previously high prevalence of Lucke renal tumor were studied. In the past decade, incidence averaged 4.2% in 29 collections (total, 1,870 frogs). No tumors were detected in 685 frogs autopsied in the

autumn of 1977 using the same method as in previous studies. Frog collections, each comprised of 20 or more animals, were compared for the presence or absence of tumor-bearing frogs. Significantly fewer collections contained tumor-bearing frogs in the autumn of 1977 than did previous collections. The decrease in tumor incidence may be due to the recent decline in the frog population in Minnesota; the spread of Lucke herpesvirus, the etiologic agent responsible for the tumor, is probably density-dependent. (20 refs)

79-7170 Gastric Remnant Carcinoma. (Eng) Klarfeld, J. (Dept. Medicine, Univ. Hosp. Cleveland-Case Western Reserve Univ., Cleveland, OH 44106); Resnick, G. *Cancer* 44(3): 1129-1133; 1979.

At the New York Hospital-Cornell Medical Center, 7 of 100 gastric carcinoma cases were identified as gastric remnant carcinoma and were analyzed and compared with prior reports in the literature. Gastric remnant carcinoma is noted in greatest incidence beginning approx 15 yr after surgery for benign gastric disease. The average age at time of diagnosis was 73 yr, with an average interval of 21.6 yr between surgery and tumor diagnosis. Only one of the seven patients was female. Although the etiology of this cancer is unknown, the high incidence of bile reflux and concomitant existence of histologic change may account for a premalignant environment in which the stomach assumes some absorptive function. Such new activity may result in the influx of potentially carcinogenic compounds and subsequent tumor development. Early diagnosis of remnant carcinoma following gastric surgery is important to improved prognosis, and endoscopic follow-up is recommended for all such patients beginning 10-15 yr postoperatively. (27 refs)

79-7171 Changing Trends and Prognostic Features in Endometrial Cancer Associated with Exogenous Estrogen Therapy. (Eng) Robboy, S. J. (Dept. Pathology, Massachusetts General Hosp., Boston, MA 02114); Bradley, R. *Obstet Gynecol* 54(3): 269-277; 1979.

Trends in the microscopic patterns of endometrial carcinoma were studied, and the biologic characteristics of cases associated with estrogen use were compared with those not associated with estrogen use. After each case was reviewed independently and in a random order by at least two pathologists, a diagnosis of cancer was agreed on in 274 patients who had been treated by five gynecologists at the Massachusetts General Hospital between 1940 and 1971. Six microscopic patterns were identified (adenocarcinoma, adenoacanthoma, atypical adenoacanthoma, adenosquamous carcinoma, clear-cell adenocarcinoma, and undifferentiated carcinoma). The frequency of each pattern relative to the other five changed only slightly during the 30-yr interval. The tumors that developed in estrogen users were more highly differentiated than those that developed in nonusers ($p < 0.005$) and were found at an earlier average age ($p < 0.02$). That the adenoacanthoma was associated with estrogen use more frequently (51%) than any other tumor type ($p < 0.02$) may reflect, in part, a similar and lower mean age of estrogen users (56 yr) and patients with adenoacanthoma (55 yr) compared with that of nonusers with the other forms of tumors (60-67 yr). Although the overall 5- and 10-yr survival rates of the estrogen users were higher than those of the nonusers, the differences between the two groups disappeared when the grade of the neoplasm was considered. (38 refs)

- 79-7172 Cancer in Persons with Inherited Blood Coagulation Disorders. (Eng) Forman, W. B. (Hematology/Oncology Section, Cleveland Veterans Admin. Hosp., 10701 East Blvd., Cleveland, OH 44106). *Cancer* 44(3): 1059-1061; 1979.

A mail survey of physicians who care for individuals with a bleeding diathesis was evaluated to assess the influence of an inherited blood coagulation disorder in the development of cancer in such individuals. In an estimated population of 10,500, 61 subjects with both disorders were identified. An apparent increase in cancer incidence in the genitourinary and musculoskeletal systems was noted. However, in the largest group (hemophiliacs), the primary cancer site was similar to that seen in an age- and sex-matched population. There did not appear to be a change in the onset of metastatic disease in individuals suffering from blood coagulation disorders, as compared to other cancer patients. (8 refs)

- 79-7173 Reduced Incidence of Endometrial Cancer Among Postmenopausal Women Treated with Progestogens. (Eng) Gambrell, R. D. (Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA 30912); Massey, F. M.; Castaneda, T. A.; Ugenas, A. J.; Ricci, C. A. *J Am Geriatr Soc* 27(9): 389-394; 1979.

A prospective study begun in 1976 to determine the incidence of endometrial cancer in postmenopausal women was undertaken to investigate the possibility of an increased risk of this disease in women receiving estrogen therapy. A retrospective study for the year 1975 was added. During 8,170 patient-years in the 3-yr 1975-1977 period, 14 endometrial malignancies were diagnosed, yielding an annual incidence of 1.7/1,000 women. During the 3,792 patient-years of observation of estrogen-progestogen users, the incidence of endometrial cancer was 0.5/1,000. The incidence of this carcinoma among estrogen users (8 cases during 2,088 patient-years) was 3.8/1,000. The difference between these two groups was statistically significant ($p < 0.01$). One adenocarcinoma was detected in a patient who had used estrogen vaginal cream for 7 mo (incidence of 1.7/1,000 during 573 patient-years of observation). In the untreated women, during 1,515 patient-years, there were 3 endometrial cancers, for an incidence of 2.0/1,000. There was no significant difference between the untreated group and the estrogen users, and only a trend ($p < 0.21$) between the estrogen-progestogen users and the untreated women. Synthetic progestogens were used to treat 199 women with endometrial hyperplasia (a precancerous lesion) for 3-6 mo. The hyperplastic endometrium reverted to normal endometrium in 96.5%. The data indicate that progestogens afford some protection against the slightly increased risk of endometrial cancer from estrogen therapy. (16 refs)

- 79-7174 Prenatal Diethylstilbestrol Exposure and Human Genital Tract Abnormalities. (Eng) Herbst, A. L. (Dept. Obstetrics and Gynecology, Univ. Chicago Medical Sch., Chicago, IL 60612); Scully, R. E.; Robboy, S. J. *Natl Cancer Inst Monogr* (51): 25-35; 1979.

By October 1975, 284 cases of clear cell carcinoma of the genital tract had been classified as vaginal (169) or cervical (115). A striking rise in the incidence of this disease began in the late 1960's and continued into the 1970's. Among 222 completely investigated cases, diethylstilbestrol (DES), dienestrol, and hexestrol had been administered to about two-thirds of the patients' mothers during pregnancy. The prescribed doses ranged from 1.5-150 mg/day.

The total amount ingested during pregnancy varied from 135 mg to 18,200 mg. In all documented cases, therapy began prior to the 18th wk of pregnancy. Ninety percent of the patients were 14 yr of age or older at the time of diagnosis. The youngest was 7 yr of age and the oldest was 28 yr of age; the median age was 18-19 yr. Most of the vaginal carcinomas were located in the upper, anterior wall. The cervical tumors primarily involved the portio. Over 93% of patients with asymptomatic tumors were rendered disease-free after surgery or radiation therapy. In exposed patients without cancer, genital tract abnormalities included vaginal adenosis, most frequently of the upper anterior or posterior walls; cervical eversion or ectropion; and transverse cervical and vaginal ridges. The prevalence of adenosis was highest in daughters exposed prior to the 8th wk of pregnancy; no cases were detected among those exposed after the 18th wk in one epidemiological study. Evidence suggests a disturbance in müllerian duct development as the cause of these changes. Whether DES is only a teratogen or also a carcinogen is unknown. No increased incidence of cancer has been documented in exposed males. (32 refs)

- 79-7175 Diet and Urinary Steroids in Black and White North American Men and Black South African Men. (Eng) Hill, P. (American Health Foundation, Naylor Dana Inst. Disease Prevention, Dana Road, Valhalla, NY 10595); Wynder, E. L.; Garbaczewski, L.; Garnes, H.; Walker, A. R. *Cancer Res* 39(12): 5101-5105; 1979.

Urinary steroid hormone content was determined in 40- to 55-yr-old Black and White North American men and rural Black South African men and in Black South African men over 60 yr of age. Some of the men were maintained on their customary diets while other Americans and Africans were transferred to a vegetarian or Western diet, respectively. When eating their customary diet, Black South African men had lower levels of urinary estrogens and androgens than did Black and White North American men. The total androgen and estrogen content decreased significantly in Black North American men on the vegetarian diet and increased in Black South African men fed a Western diet. Urinary excretion of estrogens was higher in older than in younger rural Black South African men. Data indicated that a vegetarian diet modified androgen and estrogen metabolism in North American men and that a Western diet was associated with higher levels of urinary steroid hormones in young Black South African men. Diet-related changes in steroid metabolism in rural Black South African men were age dependent. Further clarification is needed of the relationship of the increased urinary excretion of steroid hormones in Black South African men, a low-risk group fed a Western diet, and the decreased excretion in Black and White North American men, high-risk groups fed a vegetarian diet, to the development of prostatic cancer. (61 refs)

- 79-7176 Cancer Mortality Among Printing Plant Workers. (Eng) Greene, M. H. (Environmental Epidemiology Branch, NCI, Landow 3C-07, Bethesda, MD 20205); Hoover, R. N.; Eck, R. L.; Fraumeni, J. F. *Environ Res* 20(1): 66-73; 1979.

A proportionate cancer mortality study was conducted among employees of the U.S. Government Printing Office. Although the study was limited by small numbers (a total of 347 cancer deaths, among males only), there was a significantly higher proportion of deaths from multiple myeloma, leukemia, Hodgkin's disease, and colon cancer. The excess deaths from myeloma were confined to white workers in the composing room, where exposure to lead is

the major occupational hazard, while deaths from leukemia occurred primarily in bindery workers who may have had exposure to benzene. Despite methodologic limitations, these findings are consistent with other epidemiologic and experimental studies suggesting that printers are at higher risk for certain cancers. (32 refs)

- 79-7177 Smoking and Coffee Consumption in Three Groups: Cancer Deaths, Cardiovascular Deaths and Living Controls. A Prospective Study in Evans County, Georgia. (Eng) Heyden, S. (Dept. Community and Family Medicine, Duke Univ. Medical Center, Durham, NC 27710); Heyden, F.; Heiss, G.; Hames, C. G. *J Chronic Dis* 32(9/10): 673-677; 1979.

A study of 2,530 adults (60% white, 40% black) was conducted to determine whether coffee consumption and smoking habits are prospectively related to cancer mortality. Between 1967 and 1969, this population was interviewed about smoking and coffee drinking, and all deaths occurring over the next 10 yr were ascertained. Physical examinations at the start of the study indicated that the study population was free of any manifest or symptomatic cancer. Seventy-four persons died of cancer during the study period. These patients were matched with 74 patients who died of cardiovascular diseases and with 74 healthy survivors. The number of smokers among persons who died of cancer (33/74) was much greater than the number of smokers among healthy controls (22/74). Although the number of smokers in the cardiovascular group (27/74) was greater than in the control group, the difference was not so striking. There were fewer heavy coffee drinkers in the cancer group than in the cardiovascular and control groups, which had identical coffee drinking habits. These results indicate that while cigarette smoking may be related to the co-carcinogenesis in about one-third of the cancer patients, regular coffee drinking shows no relationship with carcinogenesis. (9 refs)

- 79-7178 Cancer Incidence by Marital Status: U.S. Third National Cancer Survey. (Eng) Ernster, V. L. (Dept. Epidemiology and International Health, Univ. California, San Francisco, CA 94143); Sacks, S. T.; Selvin, S.; Petrakis, N. L. *J Natl Cancer Inst* 63(3): 567-585; 1979.

Site-specific cancer incidence rates were computed separately for whites and blacks, aged 35-64 yr, by sex, age, and marital status with the use of population-based incidence data from the Third National Cancer Survey (1969-71) and with demographic data from the 1970 U.S. Census. Although rates were presented for all cancer sites combined and for 44 specific sites or rubrics, discussion focused on the 17 most common cancers. Within age, race, and sex groups, patterns of cancer incidence by marital status were compared by means of standardized incidence ratios, and the consistency of marital status patterns across age groups was assessed statistically. Among the most notable findings were excess cancer rates across most sites and age groups in single black males, consistently high rates for cancer of the lung and bronchus in divorced white males and in single black females, low rates for the hormone-dependent reproductive tumors (prostate gland, breast, uterine corpus, and ovary) in separated white males and females, and high rates for cervical cancer among separated white women. Marital status patterns, where found, frequently differed between whites and blacks and between males and females. (11 refs)

- 79-7179 Lung Cancer in Louisiana: Death Certificate Analysis. (Eng) Gottlieb, M. S. (Dept. Medicine, Tulane Univ. Medical Center, 1430 Tulane Ave., New Orleans,

LA 70112); Pickle, L. W.; Blot, W. J.; Fraumeni, J. F. *J Natl Cancer Inst* 63(5): 1131-1137; 1979.

Death certificates of residents in a cluster of Louisiana parishes (mainly in the southern part of the state), where lung cancer mortality was high, were reviewed. A comparison of the statements on occupation for 3,327 patients with lung cancer and those of 3,327 controls (matched by sex, race, age, and parish of residence) between 1960 and 1975 revealed an approx twofold excess risk associated with transportation equipment manufacture, mainly shipbuilding, and the fishing industry. Smaller elevations of lung cancer risk were found among older men who had been employed in petroleum exploration and production and among male and female residents of towns where the petroleum industry was a major employer. In addition, Acadian ancestry was associated with a higher risk of lung cancer among older men and women. (26 refs)

- 79-7180 Incidence of Nasopharyngeal Carcinoma in Malaysia, 1968-1977. (Eng) Armstrong, R. W. (ICMR, Inst. Medical Res., Univ. California, San Francisco, CA 94143); Kannan Kutty, M.; Dharmalingam, S. K.; Ponnudurai, J. R. *Br J Cancer* 40(4): 557-567; 1979.

The incidence of nasopharyngeal carcinoma (NPC) in Malaysia occurring between 1968 and 1977 was investigated. During this period, there were 2,297 confirmed cases of NPC, 1,335 of which occurred between 1973 and 1977. Age-adjusted incidence rates among Chinese male and female patients were 2.3 and 0.7 per 100,000, and that among Indian male patients was 1.0 per 100,000. There were no significant changes in incidence rates by sex or ethnic group or among the Chinese subethnic groups during the 10-yr period. In the Chinese subethnic groups, rates were highest among the Cantonese, moderate among the Khek, and lowest among the Hokkien and Teochiu. Standardized incidence ratios using Selangor as the standard population indicated considerable under-reporting in the less urban states of Malaysia, particularly among women. In Selangor, incidence rates were similar among urban and rural residents, but the frequency of cases was higher among Chinese working in factories and living in poor neighborhoods. (12 refs)

- 79-7181 Asbestos, Dental X-Rays, Tobacco, and Alcohol in the Epidemiology of Laryngeal Cancer. (Eng) Hinds, M. W. (Cancer Center Hawaii, Univ. Hawaii, 1236 Lauhala, Suite 407, Honolulu, HI 96813); Thomas, D. B.; O'Reilly, H. P. *Cancer* 44(3): 1114-1120; 1979.

A case-control study of 47 laryngeal cancers in males from three Washington state counties was conducted. Personal interview was used to obtain information on smoking, alcohol use, exposure to asbestos and other potentially harmful substances, and x-rays of the head and neck area. Smoking and alcohol consumption were found to increase risk of laryngeal cancer independently, with a clear dose-response relationship. Neither asbestos exposure nor exposure to other substances caused significant increases in the risk of laryngeal cancer, although the relative risk with asbestos exposure was 1.75. Lifetime history of exposure to dental x-rays on five or more occasions was associated with significantly increased risk of laryngeal cancer among heavy smokers but not among light smokers. The importance of tobacco and alcohol in the epidemiology of laryngeal cancer was reaffirmed, the importance of asbestos exposure was brought into question, and a possible

relationship between laryngeal cancer and exposure to dental x-rays among heavy smokers was demonstrated. (22 refs)

- 79-7182 Incidence of *Fusarium* Species and the Mycotoxins, Deoxynivalenol and Zearalenone, in Corn Produced in Esophageal Cancer Areas in Transkei. (Eng) Marasas, W. F. (National Res. Inst. Nutritional Diseases, S. African Medical Res. Council, Tygerberg 7505, S. Africa); van Rensburg, S. J.; Mirocha, C. J. *J Agric Food Chem* 27(5): 1108-1112; 1979.

The highest known esophageal cancer rate in Africa occurs in the southwestern districts of the Republic of Transkei, while the rate in the northeastern region of the country is relatively low. Corn is the main dietary staple in both areas. Three species of *Fusarium*, *F. graminearum*, *F. verticillioides* (= *F. moniliforme*) and *F. sacchari* var. *Subglutinans* (= *F. moniliforme* var. *subglutinans*), were isolated from corn kernels from both areas. Two *Fusarium* mycotoxins, deoxynivalenol and zearalenone, were detected at biologically significant levels (250-4,000 and 1,500-10,000 µg/kg, respectively) in hand-selected, visibly infected corn kernels from both areas. The level of natural contamination of corn kernels with both mycotoxins was considerably higher in the high-incidence area of esophageal cancer than in the low-incidence area. The validity of this difference could not be tested because only a small number of pooled samples were analyzed. (38 refs)

- 79-7183 Gastric Cancer Incidence. Suggestive Evidence for Persisting Effects of Experiences During 1940-1950 (World War II and Postwar Among Eastern European Immigrants to Israel and in Warsaw and Rural Poland. (Eng) Goldsmith, J. R. (Epidemiological Studies Lab., California State Health Dept., Berkeley, CA 94704); Steinitz, R.; Wronkowski, Z. *Front Gastrointest Res* 4: 111-121; 1979.

The hypothesis that the gastric cancer (GC) excess among East European immigrants to Israel might be a reflection of wartime malnutrition was studied. Age-specific incidence rates for GC among migrants from Poland, Rumania, and the Soviet Union resembled comparable rates a decade later for persons living in Warsaw and rural Poland. These rates were higher than those among persons migrating to Israel from other and poorer countries. More recent migrants showed higher age-specific incidence rates than earlier migrants. Among persons aged more than 55 yr, the slope of the age-specific incidence rates with age was steeper than among younger persons. The phenomenon was especially prominent in males and appeared to be related to the relative proportion of "intestinal" type tumors which dominate among Warsaw men aged more than 55 yr. Both immigrants who were in refugee status or concentration camps and the Polish population suffered severe nutritional and other deprivations during and immediately after World War II. A rapid decrease in most of the age-specific rates occurred in both populations during 1963-1972, but

the end of severe nutritional deprivation was in the late 1940's for most of the immigrants and in the early 1950's for the Polish populations. The findings are consistent with persisting effects of experiences during 1940-1950. (20 refs)

- 79-7184 Causes of Death of Blue-Collar Workers at a Dublin Brewery, 1954-73. (Eng) Dean, G. (Medico-Social Res. Board, Dublin, Ireland); MacLennan, R.; McLoughlin, H.; Shelley, E. *Br J Cancer* 40(4): 581-589; 1979.

The suggested association between high consumption of beer and an increased risk of death from cancer of the colon and rectum was investigated among blue-collar workers at a Dublin brewery, who consume more than average amounts of beer, usually in the form of stout. A study of their mortality between 1954 and 1973 showed that they had as good an expectation of life as all Dublin males, with no increased risk of death from cancer of the esophagus, pharynx, liver or from cirrhosis of the liver, accidents or suicide, conditions normally associated with the high consumption of alcohol. Compared with all Dublin males, they had a significantly increased risk of death from cancer of the rectum and also from diabetes mellitus. Within the brewery, the number of deaths from rectal cancer was significantly higher among men who worked in the brewhouse as opposed to other areas. (9 refs)

- 79-7185 Premalignant Lesions of the Cervix in Women of Cali, Colombia. (Eng) Duque, E. (Dept. Pathology, Sch. Medicine, Universidad del Valle, Cali, Colombia); Cuello, C.; Aristizabal, N.; Haenszel, W.; Botero, S.; Correa, P. *J Natl Cancer Inst* 63(4): 953-963; 1979.

A detailed histologic study of the uterine cervix was performed on 441 autopsy specimens from the population of Cali, Colombia, where there is one of the highest registered incidence rates of cancer at this site. The following lesions (in order of prevalence) in adult women: cervicitis, 79%; reserve cell hyperplasia, 14%; squamous metaplasia, 41%; dysplasia, 9%. Contrary to expectations, no correlation was found between increase in prevalence of these lesions and age, lower socioeconomic status, or number of pregnancies. A similar study of a sample of hysterectomies performed for uterine prolapse showed approx the same results. The findings suggest that promoting factors are more important than initiating factors in carcinogenesis of the uterine cervix. (13 refs)

See also:

- *(Rev.): 79-6603, 79-6614, 79-6615, 79-6618, 79-6625, 79-6627, 79-6639, 79-6640, 79-6641, 79-6642.
*(Chem.): 79-6663, 79-6694, 79-6696, 79-6786, 79-6840.
*(Path.): 79-7105, 79-7121, 79-7136.

MISCELLANEOUS

- 79-7186 Somatic Cell Genetic Analysis of Gene Transfer in Mammalian Cells. (Eng) Ruddle, F. H. (Dept. Biology, Yale Univ., New Haven, CT 06520); Fournier, R. E. *Brookhaven Symp Biol* (29): 96-105; 1978.

Studies of gene transfer in mammalian cells are reviewed. In gene transfer experiments, donor chromosomes are ingested by phagocytosis and degraded in lysosomes. In some instances, small fragments of the donor chromosomes avoid destruction and escape from the endocytosis apparatus. These fragments have been termed transgenomes, and their size has been estimated at 2×10^3 - 1×10^6 nucleotide base-pairs. In gene transfer studies, transferred clones could be classified as being either stable or unstable with regard to their capacity to retain the transgenome in the absence of selection pressure for its retention. It was postulated that stability might be associated with integration of the transgenome into the host-cell genome. Specific mapping of the presumed integration sites was performed using the methods of somatic cell genetics in a system in which human cells serve as the donor and mouse cells as the recipient (HuHPRT + MoHPRT-). The results of these experiments supported the hypothesis that in stable transformants, the transgenome is stably integrated into one or more sites in the recipient genome. The data also suggested that integration does not preferentially occur at the homologous locus. The experiments showed only an association between the human transgenome and specific murine chromosomes. Such an association does not provide proof of linear insertion by covalent bonding of donor DNA into host chromosomes. (20 refs)

- 79-7187 Loss of Epidermal Growth Factor Requirement and Malignant Transformation. (Eng) Cherington, P. V. (Lab. Tumor Biology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA 02115); Smith, B. L.; Pardee, A. B. *Proc Natl Acad Sci USA* 76(8): 3937-3941; 1979.

Serum provides growth factors that regulate and limit the growth of normal cells in tissue culture. Animal cells that are malignantly transformed usually exhibit diminished serum requirements for growth in culture. A defined, serum-free medium was used to determine which of these growth factors becomes dispensable for the growth of transformed Syrian and Chinese hamster fibroblast cells. The medium's four growth factors - epidermal growth factor (EGF), insulin, fibroblast growth factor, and transferrin - were added or omitted as desired. A decreased requirement for EGF was most closely related to tumorigenicity of chemically (ethylmethanesulfonate) transformed cells in nude mice. All lines examined retained their requirement for transferrin, which is needed throughout the growth cycle, in contrast to the other factors, which are needed primarily in the G₁ phase. Lines that had lost their EGF requirement but had retained their insulin requirement were arrested in G₁ by insulin deficiency, indicating that their growth control system remained. Mutagenesis with ethyl methanesulfonate can also create requirements of the transformed cells for unknown factors in serum. It is concluded that an initial step that reduces the serum requirement in culture, and in tumorigenesis, is relaxation of the growth-regulatory function of EGF. (31 refs)

- 79-7188 Significance of Specific-Locus Germ-Cell Mutations in Mice. (Eng) Bateman, A. J. (Paterson Labs., Wilmslow Rd., Manchester, England). *Mutat Res* 64(5): 345-351; 1979.

The numerical requirements of the specific-locus germ-cell mutagenicity test in the laboratory mouse were analyzed. This is the most appropriate test for the detection of gene mutations in the germ cells of a mammal, is technically simple, but requires many animals to obtain significant results. On the basis of a historical-control incidence of 39 mutants in 688,921 progeny (0.82 mutations/locus/ 10^6 gametes), it is recommended that 25,000 control progeny be included in each test. This would also be the number required from treated males, unless significantly positive results had been obtained with smaller numbers: 1 mutant in <900 progeny, 2 in <6,300, 3 in <14,500, or 4 in <24,000. In any of these events, mutagenic activity would be established in the treated series, provided that the control series comprised 25,000 with <4 mutants. Analysis of one series of mutagenicity tests indicated that post-spermatogonial stages (especially postmeiotic stages) are very sensitive to mutagens. This high sensitivity may make the post-spermatogonial stages, in spite of technical difficulties in sampling, more suitable than the spermatogonial stage for the detection of mutagens, but not for quantitative studies. (4 refs)

- 79-7189 Human Chorionic Gonadotropin α -Subunit from Cultured Choriocarcinoma (JEG) Cells: Comparison of the Subunit Secreted Free with That Prepared from Secreted Human Chorionic Gonadotropin. (Eng) Benveniste, R. (Gynecological Endocrinological Labs., Dept. Obstetrics and Gynecology, Michael Reese Medical Center, Univ. Chicago, Chicago, IL 60616); Lindner, J.; Puett, D.; Rabin, D. *Endocrinology* 105(3): 581-587; 1979.

The human chorionic gonadotropin α -subunit (JEG- α) secreted free from cultured choriocarcinoma (JEG) cells was compared with the α -subunit prepared from secreted human chorionic gonadotropin (hCG). Free JEG- α had an apparent mol wt larger than either JEG-hCG- α or standard hCG- α , the latter two being similar. JEG- α contained a major component of pI 4.8 (acid isoelectric pH) that was not present in the α -subunits derived from JEG-hCG or standard hCG. In tests of recombination with the β -subunit of hCG, freely secreted JEG- α appeared nearly incapable of forming radioreceptor assay-active hCG. A kinetic study of in vitro hCG formation over a 24-hr period confirmed that standard hCG- α and JEG-hCG- α have the ability to form an hCG which competes with hCG tracer, as contrasted with the inability of JEG- α to do so. JEG- α appeared unable to combine with standard hCG- β . These data suggest that JEG cells secrete an α -subunit in the free state that is different from the "normal" hCG α -subunit secreted by and incorporated into these same cells, as well as from that of the hCG secreted in pregnancy. (37 refs)

- 79-7190 Tumor-specific DNA Sequences in Human Gliomas. (Eng) Cuatrecasas, W. (P.O. Box 1666, Idaho Falls, ID 83401); Cho, J. R. *Cancer* 44(4): 1309-1314; 1979.

By hydroxyapatite chromatography, normal cellular DNAs were used to recycle off the repeat or normal sequences found in [3 H]DNA copied off 70S RNA from malignant human astrocytomas. The recycled DNA was then used to hybridize with DNA from normal human brain tissues and DNAs from malignant or grade IV astrocytomas. About 60%-70% of the sequences found in the 70S DNAs were normal or repeat sequences. An 88% hybridization was achieved with DNAs from malignant astrocytomas and recycled 70S DNA probes from malignant astrocytomas. Only 7% hybridization was obtained using normal brain tissue DNA. When recycled medulloblastoma 70S DNA probes were used, the percent hybridization was 67% with Grade IV astrocytoma DNA and 7% with normal brain tissue DNA. The data indicate that malignant human gliomas contain tumor-specific DNA sequences that are absent from normal brain tissues and suggest that the presence of these sequences signifies the existence of a neoplastic process. (16 refs)

- 79-7191 Differences in the Distribution of Poly(A) Size Classes in Individual Messenger RNAs from Neuroblastoma Cells. (Eng) Morrison, M. R. (Leland Fikes Lab. Cellular Neurobiology, Dept. Neurology, Univ. Texas Health Science Center at Dallas, Dallas, TX 75235); Brodeur, R.; Pardue, S.; Baskin, F.; Hall, C. L.; Rosenberg, R. N. *J Biol Chem* 254(16): 7675-7683; 1979.

The adenylated and nonadenylated messenger RNA (mRNA) populations in neuroblastoma cells were studied. Neuroblastoma polysomal mRNAs were fractionated into four classes containing poly(A) of different av lengths, using oligo(dT)-cellulose and Millipore filter techniques. Quantitation of the biological activity of each fraction in a wheat germ translation system showed that 32% of the mRNAs contained no oligo(A)s longer than 6 nucleotides, 4% had poly(A)s between 6 and 20 nucleotides, 22% had poly(A)s between 20 and 50 nucleotides, and 42% had poly(A)s with >50 nucleotides. Most mRNAs were found in each of the four size class populations, although the distribution of some individual mRNAs varied widely. The α - and β -tubulin mRNAs were more abundant in the population with long poly(A)s, whereas a significant proportion of the mRNAs coding for actin and the R₁ and R₂ cAMP-binding proteins were nonadenylated. The histone mRNAs were unique in that they were more abundant in nonadenylated mRNAs than in mRNAs containing short stretches of poly(A). The results suggest that the poly(A) termini in some mRNA species are cleaved more rapidly than those in others. (51 refs)

- 79-7192 Effect of Temperature on Protein and Immunoglobulin Synthesis and Secretion in Two Mouse Myeloma Cell Lines. (Eng) Craig, N. (Dept. Biological Sciences, Univ. Maryland Baltimore County, Catonsville, MD 21228). *J Cell Physiol* 100(2): 323-334; 1979.

Protein synthesis was studied in differentiated MOPC-21 and MPC-11 mouse myeloma cells to determine the basis for differences in temperature and actinomycin D sensitivity of translation between nondifferentiated mouse L-cells and differentiated rabbit reticulocytes. The temperature dependence of total protein synthesis was similar to that of L-cells and reticulocytes, being biphasic in Arrhenius plots with apparent activation energies of approx 25 and 42 kcal/mol, above and below 25 C. The dependence of the secretion process was different, since it was not biphasic, having a single activation energy of about 22 kcal/mol.

Myeloma polysomes were like L-cell polysomes in their response to lower temperature and reached a minimum level of 50% at 15 C. This response was also found for the specific polysomes synthesizing the IgG H- and L-chains. In the presence of actinomycin D, myeloma polysomes declined exponentially with a half-life of approx 6 hr. These two L-cell-like responses were not found in reticulocytes. Translation of both the IgG messenger RNAs (mRNAs) and the non-IgG mRNAs was reduced by lower temperatures and actinomycin D, even though the L-chain mRNA was slightly more resistant, suggesting that this mRNA is slightly more efficient. The results suggest that the translational differences between L-cells and reticulocytes are not mRNA dependent, but are cell type differences. (25 refs)

- 79-7193 Suppression of Granulopoiesis in Diffusion Chambers by Syngeneic Clonal Acute Myelogenous Leukemia Cells or Peritoneal Exudate Macrophages. (Eng) Franklin, K. W. (Div. Hematology, Peter Bent Brigham Hosp., Boston, MA); Moloney, W. C.; Greenberger, J. S. *Acta Haematol (Basel)* 61(6): 317-324; 1979.

To determine the mechanism by which acute myelogenous leukemia (AML) cells suppress normal marrow granulopoiesis, diffusion chambers containing Wistar/Furth (W/Fu) rat marrow cells, peritoneal exudate (PE) macrophages or W/Fu AML clone-3 cells were implanted ip into syngeneic irradiated rats. Growth of each population over 21 days in single or double diffusion chambers (in which cell populations were separated by a Nucleopore filter) was compared to that of mixed populations. Double diffusion chamber culture of homologous or heterologous combinations had no detectable effect on growth kinetics of any of the three cell populations as compared to single chambers. In contrast, normal granulocyte proliferation was significantly depressed by single-chamber cocultivation with equal or 10-fold lower numbers of PE macrophages or AML cells. Mixing PE macrophages with AML cells produced no preferential population suppression. AML cell differentiation was not detected under any set of conditions. These studies demonstrate that physical contact with proliferating normal macrophages as well as AML cells will suppress granulopoiesis in diffusion chambers. (26 refs)

- 79-7194 The Role of RNA and Protein Synthesis in Mediating the Action of MSH on Mouse Melanoma Cells. (Eng) Fuller, B. B. (Dept. General Biology, Univ. Arizona, Tucson, AZ 85721); Viskochil, D. H. *Life Sci* 24(26): 2405-2415; 1979.

Exposure of mouse melanoma cells in culture to MSH (melanocyte stimulating hormone) resulted in a marked increase in tyrosinase (O-diphenyl: O₂ oxidoreductase) activity following a lag period of 6-9 hr. Within 20 min after exposure of cells to MSH, the intracellular levels of cyclic AMP (cAMP) rose to levels ten times those of controls; cAMP levels then fell to twice control values by 60 min. Transient increases in rates of both protein and RNA synthesis also occurred following MSH administration and correlated in time with the dramatic but rapidly decaying increase in cellular cAMP. The increase in tyrosinase activity observed in response to either MSH, dibutyl cAMP, or theophylline was completely suppressed by the addition of either cycloheximide (0.28 μ g/ml) or actinomycin D (0.05 μ g/ml), as was the basal activity of the enzyme. Results from 14 C/ 3 H leucine studies suggest that MSH may cause increased de novo synthesis of tyrosinase. (14 refs)

- 79-7195 Incorporation of L-3,4-Dihydroxy-(2-¹⁴C)Phenylalanine into Hamster Melanoma Melanosomes. (Eng) Borovansky, J. (Dept. Chemistry and Biochemistry, Faculty General Medicine, Charles Univ., U nemocnice 5, 128 53 Prague 2, Czechoslovakia); Pavel, S.; Duchon, J.; Vulterin, K. *FEBS Lett* 104(2): 291-293; 1979.

Six Syrian hamsters bearing a transplantable Bomirski melanoma, pigmented line Ma (180th passage), were given radiolabeled L-3,4-dihydroxyphenylalanine [(2-¹⁴C)Dopa] ip and killed 4 days later. The amount of melanin in melanosomes isolated from the tumors was determined by acid hydrolysis, and radioactivity was measured by liquid scintillation spectrometry. The melanosome pellet contained about 16% of the original radioactivity. (2-¹⁴C)Dopa seemed to be tightly bound to the melanosomes. Extraction with water and exchange diffusion released no significant amount of radioactivity. However, after hydrolysis 12% of radioactivity could be detected in the hydrolyzate. These results indicate that on a subcellular level Dopa is selectively taken up by melanosomes. (25 refs)

- 79-7196 Glutamine-Phosphoribosylpyrophosphate Amidotransferase (Amidophosphoribosyltransferase, EC 2.4.2.15) Activity in Normal, Differentiating, and Neoplastic Kidney. (Eng) Prajda, N. (Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianapolis, IN 46223); Morris, H. P.; Weber, G. *Cancer Res* 39(10): 3909-3914; 1979.

The activity of glutamine-phosphoribosylpyrophosphate amidotransferase (GPA) in normal differentiating, and neoplastic (following sc transplantation of renal cell tumors) kidney was studied in male Buffalo, male ACI/N, and Wistar rats. In normal kidney cortex and in the MK-3 renal cell tumor, the pH optimum of GPA was 7.2-8.5; the Michaelis constants for glutamine were 2.0 and 1.7 mM, respectively, and the Km for MgCl₂ was 1 mM. For kidney and tumor phosphoribosylpyrophosphate, the affinities were 0.9 and 0.5 mM, respectively. The amidotransferase in the kidney showed sigmoid kinetics for phosphoribosylpyrophosphate. The 50% feedback inhibition by adenosine 5'-monophosphate of the GPA in normal kidney and in MK-3 tumor were 9.5 and 9.3 mM, respectively. The GPA-specific activities in rat thymus, testis, bone marrow, gut, kidney cortex, spleen, lung, brain, adipose tissue, heart, and skeletal muscle were 271%, 259%, 173%, 167%, 128%, 98%, 70%, 64%, 49%, 24%, and <1.0%, respectively, of that in the liver. In three transplantable renal tumors (MK-1, MK-2, and MK-3), the GPA-specific activities were increased 2.2- to 2.7-fold over that of the normal kidney cortex. During development, the av enzyme activities of 1-, 7-, 30-, and 40-day-old rats were 57%, 71%, 79%, and 114% of those in adult kidney. Elevated GPA activity should increase the capacity of the de novo purine biosynthetic pathway, and the enzyme imbalance should confer selective advantages to neoplastic cells. (37 refs)

- 79-7197 Two Major Regulatory Steps in Cholesterol Synthesis by Human Renal Cancer Cells. (Eng) Gonzalez, R. (Dept. Urologic Surgery, Univ. Minnesota, Minneapolis, MN 55455); Carlson, J. P.; Dempsey, M. E. *Arch Biochem Biophys* 196(2): 574-580; 1979.

Cholesterol synthesis was studied in a human cell line (Caki-1) established from a kidney clear cell carcinoma metastatic to skin. Exogenous cholesterol (30 µg/ml) added to the Caki-1 culture

medium decreased the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase from 270 picomoles (pmol)/min/mg with lipoprotein-poor serum to 82 pmol/min/mg. There was a rapid increase in the activity of HMG-CoA reductase when cholesterol was removed. Exogenous cholesterol decreased the incorporation into cholesterol of three labeled precursors (water, acetate, and mevalonate) three- to fivefold compared to the maximum incorporation observed in lipoprotein-poor serum. While the inhibition of cholesterol synthesis from acetate and water may be explained by the observed decrease in the activity of HMG-CoA reductase, this explanation does not hold for mevalonate. The decrease in cholesterol levels was accompanied by an increase in squalene, which suggests inhibition of cholesterol synthesis from mevalonate at the level of squalene epoxidase. Cholesterol in the presence of lipoprotein-free serum was nearly as effective as lipoprotein-bound cholesterol in lowering HMG-CoA reductase activity and blocking the conversion of acetate and mevalonate to cholesterol. The occurrence of two major mechanisms regulating cholesterol synthesis may be a unique property of renal cancer cells or a previously unrecognized general property of many cells in culture. (29 refs)

- 79-7198 Serum, Pituitary and Urine Concentrations of Prolactin and Growth Hormone in Eight Strains of Mice with Varying Incidence of Mammary Tumors. (Eng) Sinha, Y. N. (Lutcher Brown Center for Diabetes and Endocrinology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Vlahakis, G.; VanderLaan, W. P. *Int J Cancer* 24(4): 430-437; 1979.

Eight inbred strains of mice with varying incidences of spontaneous mammary tumors were compared for prolactin and growth hormone concentrations in sera, pituitary glands, and urine. Serum prolactin was compared under basal conditions as well as after stimulation with perphenazine. Both hormones were measured with specific, homologous radioimmunoassays. Although some strains having a high incidence of mammary tumors had high levels of prolactin, neither basal nor perphenazine-induced serum concentrations showed a consistent pattern that correlated with tumor incidence across mouse strains. Growth hormone levels in sera, pituitary glands, and urine also had no characteristic pattern that applied to all strains studied. The ratio of prolactin depleted from the pituitary gland to prolactin detected in serum after perphenazine injection, a reflection of the metabolic clearance rate of prolactin, was highest in two strains with a high incidence of mammary tumors and relatively lower in low-tumor strains. These results suggest that if prolactin does play a part in mammary tumor development in mice, its mechanism varies from strain to strain: while hyperprolactinemia may be the means in some strains, a peculiarity in the metabolism of the hormone may be more important in others. (28 refs)

- 79-7199 Acid Mucopolysaccharides in Mammary Tumors of Dogs. (Eng) Palmer, T. E. (Raltech Scientific Services, Inc., P. O. Box 7545, Madison, WI 53707); Monlux, A. W. *Vet Pathol* 16(5): 493-509; 1979.

Thirty-four canine mammary tumors were studied histochemically for acid mucopolysaccharide content. The tumors included ductal carcinomas (17), intraductal carcinomas (5), lobular carcinomas (2), adenomas (6), and ductal papillomas (4). Acid mucopolysaccharides of various staining intensities were seen in all tumors. The most deeply stained zones were found in cartilaginous areas. Difference in staining intensity suggested a transition from ac-

accumulated acid mucopolysaccharides to mature hyaline cartilage. Most of the mucopolysaccharides were alcian blue-positive at pH 2.5, weakly alcian blue-positive or negative at pH 1.0, periodic acid-Schiff negative, labile to hyaluronidase digestion, and stable to neuraminidase digestion. According to these characteristics, the substances were hyaluronic acid, chondroitin-4-sulfate, and chondroitin-6-sulfate. The acid mucopolysaccharides identified in the canine mammary tumors were derived from stromal or mesodermal tissues and were identical to those found in the ground substance of the matrix of normal developing hyaline cartilage. Neither the specific cell of origin nor the stimulus for acid mucopolysaccharide production in the tumors was identified. (40 refs)

79-7200 Growth of a Human Mammary Tumour Cell Line in a Serum-free Medium. (Eng) Barnes, D. (Dept. Biology Q-058, Univ. California, San Diego, La Jolla, CA 92093); Sato, G. *Nature* 281(5730): 388-389; 1979.

The growth of a human mammary tumor cell line, MCF-7, in a serum-free medium is described. MCF-7 cells could be grown, without a lag or adaptation phase, in serum-free medium supplemented with physiological levels of insulin, transferrin, epidermal growth factor (EGF), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and cold-insoluble globulin (CIg). Insulin was the most important component of the defined medium. The maximal effect of insulin was observed with 100-300 nanograms (ng)/ml with a measurable effect at 3 ng/ml. Transferrin produced a maximal stimulation at 25 μ g/ml and CIg at 7.5 μ g/ml. $PGF_{2\alpha}$ was maximally stimulatory at 100 ng/ml and EGF at 10-100 ng/ml. Cells in serum-free medium with the five factors grew as rounded clumps that were poorly attached to the dish. The addition of α -1 serum protein greatly improved attachment and spreading of MCF-7 in the serum-free medium at <1 μ g/ml. Although it is possible that long-term cultivation of MCF-7 cells in this serum-free medium may expose additional requirements for other hormones, the cells have been successfully carried for 3 mo (15 passages) in the serum-free medium. (21 refs)

LIBRARY U. OF I. URBANA - CHAMPAIGN

Author Index

- Abe, O., 79-7149
 Aboud, M., 79-6985
 Abrahamova, J., 79-7098
 Abu-Zeid, M. E., 79-6761
 Acheson, E. D., 79-6639
 Acton, A. B., 79-6604
 Adam, E., 79-7008
 Adams, R. A., 79-6822, 79-6826
 Adamson, R. H., 79-6790
 Addison, W. A., 79-6854
 Agostino, D., 79-6657
 Agostino, N., 79-6657
 Akamatsu, N., 79-6652
 Akusjarvi, G., 79-7045
 Alaba, O., 79-6991
 Alanko, K., 79-6650
 Albert, D. M., 79-7102
 Alexander, P., 79-7077
 Allaben, W. T., 79-6679
 Alsabti, E. A., 79-7161
 Althoff, J., 79-6610, 79-6721
 79-7125
 Altrock, B. W., 79-6972
 Alvarez Noves, J., 79-7051
 Alvarez Rodriguez, Y., 79-7051
 Amoroso, M., 79-7122
 Amtmann, E., 79-7003
 Anderson, D. L., 79-6944
 Anderson, G. R., 79-6994
 Anderson, S. J., 79-6964
 Anderson, S. M., 79-6948
 Anderson, T. M., 79-6818
 Andrieu, J. M., 79-7153
 Anjo, T., 79-6732
 Aoki, N., 79-6796
 Aoki, T., 79-6987
 Arady, I., 79-6698
 Archer, M. C., 79-6693
 Arendes, J., 79-7006
 Aristizabal, N., 79-7185
 Arlinghaus, R. B., 79-6990
 Armstrong, R. W., 79-7180
 Armuth, V., 79-6810
 Arnot, M. S., 79-6685
 Arnoff, B. L., 79-6855
 Arrand, J. R., 79-7024
 Arrigoni-Martelli, E., 79-7081
 Arrington, J. H., 79-6911
 Arthur, L. O., 79-6971
 Arya, S. K., 79-7052
 Asch, B. B., 79-7059
 Assa, R., 79-6667
 Asselin, J., 79-6857
 Astrin, S. M., 79-6926
 Atkins, L., 79-7126
 Auerbach, A. D., 79-6670
 Aultman, M. D., 79-7087
 Aurelian, L., 79-7009
 Austin, H., 79-7157
 Azocar, J., 79-7000
 Babcock, G. F., 79-6942
 Bacon, L. D., 79-7068
 Badowski, A., 79-7135
 Badr, F. M., 79-6671
 Badr, R. S., 79-6671
 Bailey, A. J., 79-7155
 Baird, M. B., 79-6842
 Baker, H. W., 79-6855
 Balog, B., 79-6862
 Baltimore, D., 79-6984
 Banerjee, S., 79-6664
 Banks, R. A., 79-6942
 Baptista, J., 79-7160
 Baran, N., 79-7027
 Barinsky, I. F., 79-7007
 Barker, S. T., 79-7005
 Barnes, D., 79-7200
 Barrett, A. D., 79-6983
 Barrett, T. W., 79-6606
 Basch, R. S., 79-6981
 Bases, R., 79-6925
 Baskin, F., 79-7191
 Basrur, P. K., 79-6838, 79-6845
 Bateman, A. J., 79-7188
 Batora, J., 79-6662
 Battaglini, A., 79-6672
 Batzinger, R. P., 79-6779
 Bauer, G., 79-6956
 Becci, P. J., 79-6708
 Becker, F. F., 79-6684, 79-6864
 79-7122
 Bek, V., 79-7098
 Belis, J. A., 79-6920
 Bellett, A. J., 79-7044
 Ben-Gurion, R., 79-6784
 Bendig, M. M., 79-7023
 Benhamou, J. P., 79-6616
 Benigni, R., 79-6758
 Benjamin, D. C., 79-6935
 Benn, R. T., 79-7152
 Bennett, J. M., 79-7105
 Benson, P. F., 79-6875
 Benveniste, R., 79-7189
 Ber, R., 79-6967
 Berdova, A. G., 79-7072
 Berenblum, I., 79-6810
 Berg, P., 79-7021
 Berg, S., 79-7127
 Bergsagel, D. E., 79-7155
 Berns, A., 79-6989
 Bernstein, I. D., 79-7082
 Berry, D. L., 79-6813
 Bertram, J. S., 79-6823
 Beug, H., 79-6928, 79-6929
 Bevan, D. R., 79-6831
 Beyer, J. E., 79-6773
 Bignami, M., 79-6758
 Binderup, L., 79-7081
 Bird, R. M., 79-6983
 Birnbaum, L. S., 79-6842
 Biserte, G., 79-6653
 Bishayec, S., 79-6992
 Bister, K., 79-6930, 79-7060
 Black, H. S., 79-6888
 Blattner, W. A., 79-7084
 Bloom, B. R., 79-6613
 Blot, W. J., 79-7179
 Bluestone, J. A., 79-6960
 79-7065
 Blum, H. F., 79-6627
 Blunck, J. M., 79-6757
 Boettiger, D., 79-6949
 Boggild, J., 79-7151
 Boiocchi, M., 79-6957
 Bojan, F., 79-6698
 Bolen, J. B., 79-7025
 Bolognesi, D. P., 79-7001
 Boniver, J., 79-7056
 Borek, C., 79-6630
 Borodina, N. P., 79-7020
 Borovansky, J., 79-7195
 Borzy, M. S., 79-7112
 Boshes, R. A., 79-7109
 Botero, S., 79-7185
 Boutwell, R. K., 79-6800
 Bowen, J. M., 79-6964
 Bowles, N. D., 79-6674
 Boyd, J. N., 79-6787
 Bracken, W. M., 79-6815
 Bradley, M. O., 79-6904
 Bradley, R., 79-7171
 Braman, R. S., 79-6644
 Bramm, E., 79-7081
 Brandt, L., 79-7154
 Branger, J., 79-6735
 Bresnick, E., 79-6798, 79-6828
 Brinckerhoff, C. E., 79-6795
 Brock, E. J., 79-6935
 Brodeur, R., 79-7191
 Broitman, S. A., 79-6841
 Brooks, C. L., 79-6818
 Brooks, G. P., 79-6916
 Brown, C. K., 79-6818
 Brown, J. P., 79-6957
 Brown, R. S., 79-7127
 Brown, S., 79-7002
 Brugge, J. S., 79-6936
 Brunk, G., 79-6726
 Bryan, M. E., 79-6915
 Buchanan, R. L., 79-6614
 Buecheler, J., 79-6709
 Bueding, E., 79-6779
 Buening, M. K., 79-6861
 Bulay, O., 79-6868
 Bulbrook, R. D., 79-7149
 79-7150
 Bull, A. W., 79-6860
 Burger, D. R., 79-7086
 Burke, D. C., 79-6983
 Burnette, W. N., 79-6959
 Butel, J. S., 79-6969
 Campora, J. L., 79-6919
 Capurro, P. U., 79-7165
 Carbonelle, E., 79-6785
 Cardiff, R. D., 79-6972
 Carere, A., 79-6758
 Carlson, J. P., 79-7197
 Carreon, R. M., 79-6773
 Carrier, W. L., 79-6890
 Carter, J. R., 79-6913
 Carter, W. A., 79-7052
 Carubelli, R., 79-6817
 Castaneda, T. A., 79-7173
 Castegnaro, M., 79-6722
 Cavalier, C., 79-6695
 Cerutti, P. A., 79-6859
 Cha, Y. N., 79-6779
 Challoner, A. V., 79-6892
 Chan, E. W., 79-6975
 Chan, W. C., 79-7111
 Chatelin, C. L., 79-6919
 Chen, C. J., 79-7141
 Chen, L. B., 79-7042
 Cheng, D. S., 79-7164
 Cherepantseva, E. A., 79-6940
 Cherington, P. V., 79-7187
 Chiron, J. P., 79-7063
 Chiu, J. F., 79-7094
 Chizhevskaya, V. I., 79-7020
 Cho, J. R., 79-7190
 Chowdhury, K., 79-7003
 Christopherson, W. M., 79-7136
 Chu, F. S., 79-6789
 Cianciolo, G. J., 79-7095
 Civin, C. I., 79-6878
 Clapp, N. K., 79-6674
 Clarke, E. A., 79-7156
 Clayman, C. H., 79-6944
 Claydon, D. B., 79-6620
 Clemmesen, J., 79-7151
 Clough, W., 79-7014
 Cochran, A. J., 79-6967
 Coezy, E., 79-6858
 Coggin, J. H., 79-7040
 Cohen, A. J., 79-7127
 Cohen, J. C., 79-6961
 Cole, P., 79-7157
 Collett, M. S., 79-6936
 Collins, M. J., 79-7070
 Colyer, R. A., 79-7116
 Commer, P., 79-7094
 Comoglio, P. M., 79-6950
 Conney, A. H., 79-6861
 Conran, P. B., 79-6731
 Conscience, J. F., 79-6929
 Consigli, R. A., 79-7025
 Conti, G., 79-6758
 Conti, L., 79-6758
 Cook, J. L., 79-7064
 Cooper, H. K., 79-6709
 Corbett, M. F., 79-6892
 Correa, P., 79-6692, 79-6790
 79-7185
 Corwin, L. M., 79-6841
 Costanzi, J. J., 79-7130
 Cotter, S. M., 79-7163
 Coursaget, P., 79-7063
 Coutinho, W. G., 79-6968
 Craig, A. W., 79-6724
 Craig, N., 79-7192
 Craighead, J. E., 79-6824
 79-6825
 Cram, L. S., 79-6645
 Crawford, G. M., 79-7134
 Crebelli, R., 79-6758
 Crombie, I. K., 79-7148
 Crowe, R. M., 79-6797
 Cuatico, W., 79-7190
 Cuello, C., 79-6692, 79-7185
 Currie, G. A., 79-7077
 Curtin, N. J., 79-6724
 Curtis, G., 79-6829, 79-6839
 Czernielewski, A., 79-6663
 Daich, P. B., 79-7162
 Dalgard, D. W., 79-6790
 Das, M. R., 79-6970
 Davey, G. C., 79-7077
 Davidson, N., 79-7022, 79-7027
 Davies, P. J., 79-6933
 Davies, R. E., 79-6624, 79-6884
 79-6889
 Davis, A., 79-6892
 Davis, J., 79-6964
 Davis, S., 79-7076
 Day, E. W., 79-6729
 De Martino, A. M., 79-6615
 De Mattheis, M. C., 79-6840
 Dean, B. J., 79-6744
 Dean, G., 79-7184
 Dean, J. H., 79-7084
 Decha-umphai, W., 79-7094
 Declève, A., 79-7056
 deHarven, E., 79-6979
 Dei, T., 79-7066, 79-7092
 Deknudt, G., 79-6646
 DeMendonca, W., 79-7112
 Dempsey, M. E., 79-7197
 den Hertog, A., 79-6661
 Denenberg, B., 79-6818
 Denis, F., 79-7063
 Denlinger, R. H., 79-6608
 Deshayes, P., 79-6908
 Desjardins, C., 79-7137
 Dessauw, P., 79-6908
 Desselberger, U., 79-7028
 Dharmalingam, S. K., 79-7180
 Diamond, L., 79-6793
 Dictor, M., 79-7112
 Dierks, P. M., 79-6953
 Diessner, H., 79-6709
 Diffey, B. L., 79-6892
 DiGiovanni, J., 79-6807
 79-6813
 Dikshtein, E. A., 79-7128
 Dion, A. S., 79-6962, 79-6968
 Diop Mar, I., 79-7063
 DiPaolo, J. A., 79-6891
 79-7159
 Dipple, A., 79-6740, 79-6804
 79-6805
 Dittenber, D. D., 79-6677
 Divertie, M. B., 79-6896
 Dixon, F. J., 79-7085
 Doderlein, G., 79-6929
 Doerger, G., 79-6865
 Dogliotti, E., 79-6758
 Dolev, S., 79-6985
 Domina, A. H., 79-7132
 Donnelly, T., 79-6728
 Donner, A., 79-7156
 Donovan, P. J., 79-6891
 79-7159
 Dorney, D. J., 79-6877
 Dorsch-Hasler, K., 79-6801
 Dostalova, V., 79-6946
 Drescher, J., 79-7028
 Drucker, J., 79-7063
 Drysdale, H. C., 79-7107

- Ducastelle, C., 79-6908
Duchon, J., 79-7195
Duesberg, P. H., 79-6930
79-7060
Duncan, S. C., 79-7158
Dunlop, N. M., 79-7001
Duque, E., 79-7185
Dusing-Swartz, S., 79-6969
Dworsky, R., 79-7160
Eastman, A., 79-6828
Eaton, M. D., 79-7061
Ecanow, B., 79-6632
Ecanow, C., 79-6632
Eck, R. L., 79-7176
Eckardt, F., 79-6869
Eckhart, W., 79-7026
Edwards, G. S., 79-6696
Eaton, M. D., 79-6927
Eisenman, R. N., 79-6937
Ekstedt, R. D., 79-7080
El Abed, A., 79-6811
Elejalde, B. R., 79-6637
Elequin, F., 79-6925
Elkind, M. M., 79-6871
Elkon, D., 79-6918
Ellis, R. W., 79-6958
Elwood, J. M., 79-7134
Emura, M., 79-6725
Engel, D., 79-6906
Enouf, J., 79-6939
Eremina, L. A., 79-7020
Erikson, R. L., 79-6936
Ernst, V. L., 79-7178
Essex, M., 79-7000, 79-7163
Exon, J. H., 79-6651
Ezdinli, E. Z., 79-7088
Ezoe, H., 79-7050
Fabry, L., 79-6785
Fahey, J. V., 79-6795
Falk, H. L., 79-6715
Falke, D., 79-7006
Famulari, N., 79-6958
Faras, A. J., 79-6936, 79-6944
Farber, E., 79-6779, 79-7123
Fears, T. R., 79-7168
Feorino, P. M., 79-7013
Ferlito, A., 79-6909
Ferm, R. R., 79-6900
Ferm, V. H., 79-6900
Feron, V. J., 79-6678
Festa, R. S., 79-7109
Fine, D. H., 79-6696
Finerman, G. A., 79-7117
Finkel, M. P., 79-6975
Fischer, S. M., 79-6800
Fischer, W., 79-6682
Fischinger, P. J., 79-7001
Fish, J. E., 79-6896
Fisher, M. S., 79-6878, 79-6879
79-6887
Fisher, P. B., 79-6801
Fissore, A., 79-6919
Fissore, O., 79-6919
Fleissner, E., 79-6958
Fohring, B., 79-7047
Folk, W. R., 79-7023
Folse, D. S., 79-6756
Forbes, P. D., 79-6881, 79-6884
79-6889
Forman, W. B., 79-7172
Forsberg, J. G., 79-6852
Fournier, M., 79-7069
Fournier, R. E., 79-7186
Fout, G. S., 79-6962
Fox, C. H., 79-6832
Fox, O. F., 79-6817
Francis, D. P., 79-7163
Francke, U., 79-7002, 79-7126
Frank, H., 79-7001
Franklin, K. W., 79-7193
Fraumeni, J. F., 79-7084
79-7176, 79-7179
Freedman, H. J., 79-6819
Freel, R. J., 79-7111
Freeman, R. G., 79-6882
Frei, J. V., 79-6712
Freitag, F., 79-6912
Fried, R., 79-7132
Friedman, A. H., 79-7102
Friis, R. R., 79-6934
Fry, R. J., 79-6872
Fu, Y. S., 79-6913
Fujiki, H., 79-6844
Fuller, B. B., 79-7194
Furuya, T., 79-6776
Fusco, J. C., 79-6723
Fusenig, N. E., 79-6809
Gaede, J. T., 79-7114
Gagnon, H. J., 79-6672
Gallie, B. L., 79-7101
Gallimore, P. H., 79-7042
Gambrell, R. D., 79-7173
Garbaczewski, L., 79-7175
Gardner, H. A., 79-7101
Gardner, M. J., 79-6639
Garnes, H., 79-7175
Garren, L., 79-6722
Garrison, C., 79-6894
Gart, J. J., 79-7159
Gaugler, B. J., 79-6848
Gazdar, A. F., 79-7002
Geary, C. G., 79-7152
Gehring, P. J., 79-6773
Geis, A., 79-7047
Geissler, E., 79-7037, 79-7039
Georgii, A., 79-7028
Gerber, G. B., 79-6646
Gerlach, H., 79-6902
Gershwin, M. E., 79-7118
Geser, A., 79-7013
Getaz, E. P., 79-7166
Giacomoni, D., 79-7055
Giannelli, F., 79-6875
Gierek, T., 79-7090
Gilbert, E., 79-7112
Gilboa, E., 79-6984
Gingell, R., 79-6726
Ginsberg, H. S., 79-6801
Glasenapp, G. B., 79-6912
Gleason, G. L., 79-6800
79-6827
Glober, G., 79-7149
Gluszczyk, M., 79-6663
Godefroy-Colburn, T., 79-7053
79-7054
Goff, S., 79-6984
Gold, B. H., 79-6632
Goldfarb, M. P., 79-6982
Goldschmidt, B. M., 79-6666
Goldsmith, J. R., 79-7183
Gomez, G. A., 79-7108
Gonzalez, R., 79-7197
Good, R. A., 79-7097
Goodrich-Smith, M., 79-6818
Goodwin, P. R., 79-7149
Gordillo, G., 79-6692
Gorham, E., 79-7169
Gorham, L. S., 79-6923
Gorzinski, S. J., 79-6677
Gottlieb, M. S., 79-7179
Goudeau, A., 79-7063
Grabowski, W., 79-6836
Grace, D. R., 79-6896
Graf, T., 79-6928, 79-6929
79-6931
Graham, F. L., 79-7046
Graic, Y., 79-6908
Grandjean, C., 79-6721
Grandjean, C. J., 79-6610
Grant, T. T., 79-7117
Graz, D., 79-6981
Gray, L. A., 79-7136
Greaves, M. F., 79-7107
Greenberg, B. R., 79-7118
Greenberger, J. S., 79-7193
Greene, M. H., 79-7084, 79-7086
79-7176
Greenwald, P., 79-7162
Greenwood, F. C., 79-7149
Griem, M. L., 79-7111
Griesemer, R. A., 79-6802
79-6814
Griffin, A. C., 79-6685
Griffin, B. E., 79-7024
Griffith, B. P., 79-6995
Grisham, J. W., 79-6705
Groth, K., 79-6836
Grover, P. L., 79-6808
Grozea, P. N., 79-7111
Grubbs, C. J., 79-6708
Grube, D. D., 79-6872
Grund, E., 79-6682
Grundmann, E., 79-7115
Grutman, G., 79-6785
Gualandi, G., 79-6758
Gupta, R. K., 79-7085
Gurtsoo, H. L., 79-6819
Gurtsevich, V., 79-7018
Habeshaw, J. A., 79-7078
Haddox, M. K., 79-6843
Hadlich, J., 79-6905
Haenszel, W., 79-7185
Hakura, A., 79-6947
Hall, C. L., 79-7191
Hall, M. R., 79-6952
Hamada, C., 79-7048, 79-7049
Hames, C. G., 79-7177
Hammond, C. B., 79-6854
Hammerius, Y., 79-6895
Hanafusa, H., 79-6943, 79-6948
Handleman, S., 79-6894
Hansen, J. P., 79-7147
Hansen, T. J., 79-6693
Harada, T., 79-6838, 79-6845
Hard, G. C., 79-6863
Harder, W. O., 79-6789
Hardin, L., 79-6827
Hardy, W. D., 79-7163
Hargis, B. J., 79-7041
Harris, C. C., 79-6834
Harris, E. D., 79-6795
Harris, N., 79-6981
Harris, R., 79-7074
Hart Hansen, J. P., 79-7151
Hartley, J. W., 79-7053
Hashimoto, Z., 79-7131
Hashiro, G. M., 79-7012
Haughton, G., 79-6942
Havens, M. B., 79-6819
Hayman, M. J., 79-6931
Haynes, R. H., 79-6869
Hayward, J. L., 79-7149
79-7150
Hearn, W. L., 79-6767
Heatfield, B. M., 79-6689
Heberling, R. L., 79-7005
Hecht, S. S., 79-6611, 79-6836
Heidelberg, C., 79-6883
Heiss, G., 79-7177
Hellstrom, I., 79-7082
Hellstrom, K. E., 79-7082
Hemet, J., 79-6908
Hemminki, K., 79-6704
Henderson, B. E., 79-7160
Henderson, S. V., 79-6888
Herberman, R. B., 79-6987
79-7075, 79-7084
Herbst, A. L., 79-7174
Herrmann, J., 79-6637
Hesbert, A., 79-6695
Heyden, F., 79-7177
Heyden, S., 79-7177
Higgins, J. T., 79-7124
Highfield, P. E., 79-6953
Hildebrand, C. E., 79-6645
Hildebrand, H. F., 79-6653
Hilfrich, J., 79-6611
Hilgers, J., 79-6965
Hill, P., 79-7175
Hinds, M. W., 79-7167, 79-7181
Hinton, D. E., 79-6689
Hirakawa, T., 79-6737
Hirayama, T., 79-7141
Hirose, M., 79-6687, 79-6701
Hirota, N., 79-6688
Hirota, T., 79-6917
Hlozanek, I., 79-6946
Hoare, S. A., 79-7150
Hobik, H. P., 79-7115
Hodgson, R. M., 79-6865
Hodson-Walker, G., 79-6744
Hoffbrand, A. V., 79-7107
Hoffmann, D., 79-6611
Hoffmann, E., 79-6986
Hogetveit, A. C., 79-7143
79-7144
Hohn, P., 79-6673
Hojo, K., 79-6917
Holmes, L. B., 79-7126
Holoubek, V., 79-6756
Holtzman, S., 79-6847
Homburger, F., 79-6822, 79-6826
Honeycutt, N., 79-6945
Hong, R., 79-7112
Hook, R. A., 79-7087
Hoover, E. A., 79-6999
Hoover, R. N., 79-7142, 79-7176
Hoppe, H., 79-6700
Horikami, S., 79-7012
Horoszewicz, J. S., 79-7052
Horowitz, S. D., 79-7112
Horster, H. G., 79-6770
Hoshino, H., 79-6978
Houdek, J., 79-7138
Howley, P. M., 79-6996
Hsie, A. W., 79-6723
Hsiung, G. D., 79-6995
Hsu, I. C., 79-6834
Hsu, S. D., 79-7130
Huang, C. S., 79-7108
Huber, S. A., 79-6786
Hudgins, W. R., 79-6740
Hudson, P., 79-6715
Hull, M. T., 79-7124
Hunter, E., 79-6941
Hutchinson, M. A., 79-7026
Huuskonen, M. S., 79-6650
Ihle, J. N., 79-7001
Immenkamp, M., 79-7115
Indo, K., 79-6833
Ingnot, A. D., 79-6988
Ingnot, O., 79-6988
Inui, N., 79-6835
Iriya, K., 79-6849
Isobe, M., 79-6867
Itabashi, M., 79-6917
Itaya, K., 79-7096
Ito, N., 79-6687, 79-6731
79-6816
Ito, Y., 79-7029
Ivanovic, S., 79-6607
Iwai, M., 79-6966
Iwai, Y., 79-6966
Iype, P. T., 79-6804
Jacobs, M. M., 79-6685
Jacobs, S. C., 79-7127
Jacobson, E., 79-6880
Jaenisch, R., 79-6986, 79-6989
Janisch, W., 79-6902
Jay, G., 79-6932, 79-6933
Jay, M. R., 79-7091
Jecker, L., 79-6815
Jensen, M. K., 79-6783
Jerina, D. M., 79-6861
Jhabvala, P. S., 79-7053
79-7054
Job, L., 79-7052
Johnson, P. S., 79-7104
Johnson, W., 79-6692
Jones, D. W., 79-6806
Jones, G., 79-6894
Jones, L., 79-7107
Juchau, M. R., 79-6807, 79-6813
Jurgelski, W., 79-6715
Kaiserling, E., 79-7110
Kalinis, R. P., 79-6677
Kalter, S. S., 79-7005
Kamahora, T., 79-6947
Kaminskaia, L. P., 79-7072
Kamiya, S., 79-6701

Kandzari, S. J., 79-6920
 Kannan Kutty, M., 79-7180
 Kaplan, H. S., 79-7056
 Karess, R. E., 79-6943, 79-6948
 Karle, J. M., 79-6861
 Karshin, W. L., 79-6990
 Kato, K., 79-6736
 Katyal, S. L., 79-6683
 Katz, D. A., 79-7104
 Kaufman, D., 79-7112
 Kaufman, D. G., 79-6705
 Kaufman, R. H., 79-7008
 Kaufmann, W. K., 79-6705
 Kawachi, T., 79-6690, 79-6737
 Keefer, L. K., 79-6865
 Keimes, A. M., 79-6631
 Kelly, P. A., 79-6857
 Kempner, D. H., 79-7091
 Kennedy, A. R., 79-6638
 79-6922
 Kerdelhue, B., 79-6811
 Keyes, D. G., 79-6677, 79-6773
 Khalil, A. M., 79-7146
 Khan, A. S., 79-6635
 Kiec-Swierczynska, M., 79-6663
 Kinebuchi, M., 79-6690
 Kinlen, L. J., 79-7142
 Kinzie, J. M., 79-6788
 Kirkpatrick, C. H., 79-7064
 Kishore, G. S., 79-6817
 Kitchener, G., 79-6931
 Klarfeld, J., 79-7170
 Kleihues, P., 79-6709, 79-6865
 Klein, A. K., 79-7118
 Klein, G., 79-6967, 79-7015
 79-7071
 Klein, K. K., 79-7122
 Kleinbans, C. M., 79-6888
 Klener, V., 79-6910
 Klenova, A. V., 79-7020
 Klima, W. C., 79-6674
 Kline, S. A., 79-6664
 Klink, E., 79-6727
 Kloppel, G., 79-6727
 Knight, L. A., 79-7101
 Knox, J. M., 79-6886
 Knudson, A. G., 79-6636
 Kobayashi, H., 79-6977
 Kobayashi, N., 79-6611
 Kobayashi, T., 79-7121
 Kober, O., 79-6866
 Kociba, R. J., 79-6677, 79-6773
 Koenigsberg, M., 79-6925
 Koestner, A., 79-6608
 Kohga, S., 79-7120
 Kohn, D. B., 79-6632
 Kohn, K. W., 79-6904
 Kohno, S. I., 79-7108
 Kolar, G. F., 79-6709
 Koller, L. D., 79-6651
 Kollias, N., 79-6761
 Kolodziejska, A., 79-6832
 Komura, J., 79-7030
 Kondo, S., 79-6706
 Konze-Thomas, B., 79-6877
 Koornstra, W., 79-6973
 Korinkova, P., 79-7098
 Kosiakova, N. P., 79-7058
 Koskimies, S., 79-7015
 Kourous, M., 79-6742
 Kowalski, B., 79-6722
 Koyama, H., 79-6652
 Koyama, Y., 79-6917
 Kozbor, D., 79-7015
 Krause, J. R., 79-7113
 Kreja, L., 79-6976
 Krell, K., 79-6880
 Kriek, E., 79-6680, 79-6691
 Kripke, M. L., 79-6628, 79-6878
 79-6887
 Krueger, R. G., 79-6993
 Kruger, D. H., 79-6605
 Krzyzek, R. A., 79-6936
 Kucerova, M., 79-6662
 Kuehl, W. M., 79-6935

Kugaczewska, M., 79-6832
 Kuhnert, L. K., 79-6954
 Kumaoka, S., 79-7149
 Kunze, E., 79-6733
 Kuo, K. C., 79-7141
 Kurata, Y., 79-7096
 Kurtis, B., 79-6738
 Kushner, J. P., 79-7164
 Kusnierczyk, W., 79-7090
 Kuszynski, C., 79-6829
 Kuzumaki, N., 79-6967
 Labrie, F., 79-6857
 Labuc, G. E., 79-6757
 Lagrou, C., 79-6928
 Lakowicz, J. R., 79-6831
 Lam, K. M., 79-6955
 Lamden, M., 79-6798
 Lancaster, W. D., 79-6996
 79-6998
 Langenbach, R., 79-6829
 Langley, G. R., 79-7155
 Larrick, S. B., 79-7001
 Lasfargues, E. Y., 79-6968
 Latarjet, R., 79-6876
 Latt, S. A., 79-6686
 Lau, A. F., 79-6936
 Lau, S. S., 79-6746
 Law, L. W., 79-6991
 Law, M. F., 79-6996
 Lawley, P. D., 79-6712
 Lawrence, F., 79-6939
 Lazear, E. J., 79-6679
 Le Riverend, E., 79-7018
 Leach, J. F., 79-6892
 Leck, I., 79-7152
 Lederer, E., 79-6939
 Lee, C. K., 79-6975
 Lee, I. P., 79-6668
 Lee, L. F., 79-7068
 Lee, L. S., 79-6799
 Lee, W. H., 79-6890
 Leitch, C. R., 79-6937
 Lemonnier, M., 79-6695
 Lennert, K., 79-7110
 Leonard, A., 79-6785
 LeSane, F. V., 79-7084
 Levin, W., 79-6684, 79-6861
 Levine, A. J., 79-7038, 79-7079
 Lewis, A. M., 79-7036, 79-7064
 Lewis, M. A., 79-6793
 Lewis, R., 79-7008
 Ley, R. D., 79-6872
 Li, F. P., 79-7127
 Lieberman, M., 79-7056
 Lieberman, M. W., 79-6873
 Liebeskind, D., 79-6925
 Lijinsky, W., 79-6812
 Lill, P. H., 79-6878
 Lilly, F., 79-6980
 Lin, J. C., 79-7017
 Lin, T. M., 79-7141
 Lindholm, T. S., 79-7117
 Lindner, J., 79-7189
 Linna, T. J., 79-6955
 Linse, R., 79-6905
 Lintas, C., 79-6840
 Linville, D., 79-6807
 Linzer, D. I., 79-7038
 Lipsky, M. M., 79-6689
 Lisiewicz, J., 79-7090
 Lisowe, R. W., 79-6677
 Little, J. B., 79-6638, 79-6922
 79-7102
 LiVolsi, V. A., 79-7010
 Llewellyn, G. C., 79-6788
 Lock, S., 79-6699
 Locker, E., 79-7103
 Lockman, D. S., 79-6911
 Loewengart, G., 79-6666
 Logue, G. L., 79-7114
 Loh, P. C., 79-7012
 Loliger, H. C., 79-6930
 Lombardi, B., 79-6683
 London, W. T., 79-6716
 Long, C. W., 79-6971

Lopez, C., 79-6960, 79-7065
 Lopez, J. R., 79-6761
 Lostrom, M. E., 79-6959
 Lotem, J., 79-6794
 Louie, S. C., 79-6679
 Lubbe, L., 79-7037, 79-7039
 Lucas, Z. J., 79-6786
 Luckert, P. H., 79-6675
 Lurain, J. R., 79-7133
 Lurie, A. G., 79-6731, 79-6816
 Lynch, H. T., 79-7132
 Lynch, J. F., 79-7132
 Ma, T. H., 79-6899
 MacDonald, R. N., 79-7155
 MacFarlane, J. K., 79-7093
 Mach, O., 79-6946
 Mack, T., 79-7160
 Mackova, N., 79-6914
 MacLennan, R., 79-7184
 Maekawa, A., 79-6701
 Maeta, Y., 79-7048, 79-7049
 Maera, Y., 79-7131
 Magnus, I. A., 79-6875, 79-6892
 Magnusson, G., 79-7021
 Maher, V. M., 79-6877
 Mahle, N. H., 79-6677
 Majors, J. E., 79-6961
 Majsky, A., 79-7098
 Mak, I., 79-7046, 79-7050
 Mak, S., 79-7046, 79-7050
 Makela, O., 79-7015
 Maliner, J. S., 79-6644
 Malkiel, S., 79-7041
 Maltzman, W., 79-7038
 Malunowicz, E., 79-6832
 Manor, H., 79-7022, 79-7027
 Marasas, W. F., 79-7182
 Marchetto, D. J., 79-7127
 Margison, G. P., 79-6724
 Marotti, K. R., 79-6994
 Marshall, C. J., 79-7067
 Marshall, M. V., 79-6685
 Martin, F., 79-6866
 Martin, F. B., 79-7169
 Martin, G. S., 79-6945
 Martin, M., 79-6866
 Martin, R. G., 79-7036
 Martin, S., 79-7103
 Martinez, P., 79-6761
 Maruchi, N., 79-7139
 Massey, F. M., 79-7173
 Massey, R. J., 79-6971
 Mathes, L. E., 79-6999
 Matsukura, N., 79-6690
 Matsunaga, E., 79-7100
 Matsushima, T., 79-6776
 Maupas, P., 79-7063
 May, J. T., 79-7130
 Mazariova, O., 79-6697
 McCormick, J. J., 79-6877
 McCormick, K. J., 79-7059
 McDougall, J. K., 79-7042
 McFadden, K. M., 79-6923
 McIntire, K. R., 79-6987
 McKeen, E. A., 79-7084
 McKinnell, R. G., 79-7169
 McLachlan, J. A., 79-6846
 McLoughlin, H., 79-7184
 McMillan, R. M., 79-6795
 Meade, P. D., 79-6845
 Meadows, A. T., 79-7109
 Medina, D., 79-6963, 79-6969
 Medline, A., 79-7123
 Melchionne, S., 79-6666
 Melnick, J. L., 79-7008
 Menck, H., 79-7160
 Mendez, F., 79-6925
 Mendrala, A. L., 79-6877
 Merezko, V. A., 79-7128
 Merino, M. J., 79-7010
 Merli, F., 79-6840
 Metzler, M., 79-6851
 Meunier, P., 79-6798
 Meyers, M., 79-6661
 Meyers, P., 79-6952

Michalides, R., 79-6965
 Mihailovich, N., 79-6609
 79-6748
 Mikhelson, V. M., 79-6629
 Milam, D. F., 79-6920
 Milas, L., 79-6907
 Miller, A. B., 79-7155
 Mink, M. M., 79-6970
 Minna, J. D., 79-7002
 Minowada, J., 79-6819
 Mirocha, C. J., 79-7182
 Mirra, J. M., 79-7117
 Misumi, H., 79-6938
 Mitchison, N. A., 79-6981
 Mitra, S. W., 79-6984
 Mitsumori, K., 79-6736
 Mitsuoka, T., 79-6643
 Miwa, M., 79-6796
 Miyachi, Y., 79-7030
 Miyaji, H., 79-6833
 Miyaki, M., 79-6652
 Miyamoto, M., 79-7131
 Miyamura, T., 79-7032
 Miyata, Y., 79-6687
 Miyazawa, T., 79-6736, 79-6768
 Mizumoto, S., 79-7131
 Mizutani, T., 79-6643
 Mochizuki, M., 79-6732
 Moelling, K., 79-6934
 Mohr, U., 79-6612, 79-6725
 Mollner, T., 79-6714
 Moloney, W. C., 79-7193
 Monconduit, M., 79-6908
 Mondal, S., 79-6883
 Monlux, A. W., 79-7199
 Montelaro, R. C., 79-7001
 Montes, G., 79-6692
 Montes-Rendon, A., 79-6667
 Monti-Bragadin, C., 79-6950
 Moon, R. C., 79-6708
 Moore, J. W., 79-7150
 Moore, M. A., 79-7073
 More, I. A., 79-6967
 Moreau, A., 79-6761
 Mori, M., 79-6835, 79-6844
 Mori, W., 79-7139
 Morimoto, K., 79-6707
 Moriuchi, T., 79-6977
 Moriya, M., 79-6736, 79-6768
 Moriya, Y., 79-6917
 Morris, A. G., 79-6983
 Morris, H. P., 79-7196
 Morrison, M. R., 79-7191
 Morton, D. L., 79-7085
 Morton, W. E., 79-6644
 Moschel, R. C., 79-6740
 Moscovici, C., 79-6943, 79-7060
 Mosharrafa, E. T., 79-6944
 Moss, P. S., 79-6945
 Mossman, B. T., 79-6824
 79-6825
 Moyer, M. P., 79-7035
 Moyer, R. C., 79-7035
 Mufson, R. A., 79-6800
 Mullen, E. E., 79-6935
 Muller, G., 79-6739
 Muller, J., 79-7124
 Muller, W. E., 79-7006
 Mulvihill, J. J., 79-7084
 Munhall, A., 79-6714
 Murasaki, G., 79-6687
 Murata, Y., 79-6966
 Murphy, G. P., 79-6855
 Murray, A. W., 79-6809
 Murthy, P. B., 79-6856
 Musson, D. G., 79-6734
 Nada, G. N., 79-7146
 Nagao, M., 79-6776
 Nagel, D., 79-6726
 Nakanishi, K., 79-6687
 Nakano, S., 79-6649, 79-6870
 Nakatsuka, T., 79-6816
 Nakayasu, M., 79-6796, 79-6844
 Naso, R. B., 79-6964, 79-6990
 Natarajan, A. T., 79-6661

- Nathans, D., 79-6634
National Cancer Institute
79-6647, 79-6648, 79-6654,
79-6655, 79-6656, 79-6658,
79-6659, 79-6660, 79-6665,
79-6669, 79-6676, 79-6702,
79-6711, 79-6713, 79-6717,
79-6718, 79-6719, 79-6720,
79-6730, 79-6741, 79-6747,
79-6749, 79-6750, 79-6751,
79-6752, 79-6753, 79-6754,
79-6755, 79-6759, 79-6760,
79-6762, 79-6763, 79-6764,
79-6765, 79-6766, 79-6769,
79-6772, 79-6774, 79-6775,
79-6777, 79-6778, 79-6780,
79-6792, 79-6820
Nealon, N., 79-7136
Nettesheim, P., 79-6710
79-6802, 79-6814
Neumann, H. G., 79-6848
Ng, A. K., 79-6987
Nielsen, N. H., 79-7147
79-7151
Nigro, N. D., 79-6860
Nikaido, M., 79-7030
Nime, F., 79-6855
Nisch, G., 79-7037, 79-7039
Nishi, Y., 79-6835
Niwa, O., 79-6893
Nixon, J. E., 79-6651
Nizami, F., 79-6791
Nizami, H. M., 79-6791
Nomura, K., 79-7129
Norikane, K., 79-6708
Norpoth, K., 79-6739
Nove, J., 79-7102
Novelletto, A., 79-6758
Novikoff, A. B., 79-6684
Novikoff, P. M., 79-6684
Novotna, J., 79-6910
Nowinski, R. C., 79-6957
79-6959
Numoto, S., 79-6771
Nusse, R., 79-6965
Nyfors, A., 79-6783
Nyormoi, O., 79-7019
O'Brien, T. G., 79-6793
O'Donnell, P. V., 79-6958
O'Neill, J. P., 79-6723
O'Reilly, H. P., 79-7181
O'Sullivan, D. D., 79-7088
Obata, Y., 79-7097
Obe, G., 79-6661
Ocho, M., 79-7004
Oda, T., 79-6938, 79-7004
Odashima, S., 79-6701
Ogawa, K., 79-7123
Ogino, A., 79-7030
Ogrowsky, D., 79-7125
Oguchi, M., 79-7030
Ogura, H., 79-7004
Ohta, T., 79-6768
Oie, H. K., 79-7002
Okada, M., 79-6732
Okada, S., 79-7096
Okeda, T., 79-6649
Okumoto, M., 79-6966
Oleszak, E., 79-6988
Olofsson, H., 79-6895
Olsen, R. G., 79-6999
Olsson, H., 79-7154
Ono, T., 79-6652
Ornstein, R. L., 79-6743
Ortali, V. A., 79-6758
Osborne, J. W., 79-6916
Ostertag, H., 79-7028
Otsuka, H., 79-6771
Oud, J. L., 79-6735
Owens, D. W., 79-6886
Oxelius, V. A., 79-7112
Pagman, L., 79-7112
Pagano, J. S., 79-7017
Pahnke, V. A., 79-6975
Paigen, B., 79-6819
Paika, I., 79-6672
Paika, I. J., 79-6686
Pal, K., 79-6808
Palmer, A. E., 79-6716
Palmer, T. E., 79-7199
Pandey, K. N., 79-6898
Pani, B., 79-6950
Pardee, A. B., 79-7187
Pardue, S., 79-7191
Parke, D. V., 79-6821
Parker, N. B., 79-6819
Parker, R. T., 79-6854
Parks, R. C., 79-7089
Parshad, R., 79-6894
Parsons, J. T., 79-6935
79-6953
Parsons, S. J., 79-6935
Pastan, I., 79-6932, 79-6933
Patel, N. T., 79-6756
Patil, K., 79-6868
Paucha, E., 79-7034
Pauley, R. J., 79-6963
Pavel, S., 79-7195
Pawsey, S. A., 79-6875
Pawson, T., 79-6945
Pazmino, N. H., 79-6878
Peck, R. M., 79-6723
Pegg, A. E., 79-6862
Pelon, W., 79-6692
Peng, M., 79-6696
Penman, B. W., 79-6700
Penn, R., 79-7104
Perdue, J. F., 79-6951
Perez, C., 79-6761
Perricaudet, M., 79-7045
Pesek, M., 79-7138
Pessayre, D., 79-6616
Pester, J., 79-7104
Peters, H., 79-6631
Peters, L. J., 79-6907
Petit, P., 79-7106
Petrakis, N. L., 79-7178
Pettersson, U., 79-7045
Pheps, A. W., 79-6888
Phillips, E. R., 79-6951
Pickle, L. W., 79-7179
Pickren, J. W., 79-6855
Piekarski, L., 79-6832
Pike, M. C., 79-7160
Pilch, J., 79-7090
Pinter, A., 79-6959, 79-6979
Piver, M. S., 79-7133
Plaai, D., 79-7043
Plata, F., 79-6980
Poduval, T. B., 79-7083
Polivkova, Z., 79-6662
Pollack, R., 79-6797
Pollard, M., 79-6675
Pomenti, A. A., 79-6962
Poncelet, F., 79-6785
Ponnudurai, J. R., 79-7180
Poole, T. W., 79-6821
Popov, D. K., 79-6924
Popp, F. A., 79-6601
Poppema, S., 79-7110
Poruchynsky, M. S., 79-6684
Posevaia, T. A., 79-7058
Potocki, L. J., 79-6832
Potworowski, E. F., 79-7069
Poupko, J. M., 79-6767
Pour, P., 79-6726, 79-6728
79-7125
Prajda, N., 79-7196
Praslicka, M., 79-6914
Prat, M., 79-6950
Prema, K., 79-6856
Presber, W., 79-6605
Preston-Martin, S., 79-7160
Price, F., 79-6894
Przystasz, T., 79-7135
Puccetti, P., 79-7075
Puett, D., 79-7189
Qualtiere, L. F., 79-6952
Quarles, J. M., 79-6812
Rabin, D., 79-7189
Rabouh, S. A., 79-6671
Rabson, A. S., 79-7064
Radman, M., 79-6623
Radomski, J. L., 79-6767
Rady, P., 79-6698
Raghuvarasud, P., 79-7088
Raheem, M. A., 79-7146
Raikhlin, N. T., 79-7119
Rajalakshmi, S., 79-6779
Ramabhadran, T. V., 79-7053
Ramsay, C. A., 79-6875
Rao, K. V., 79-6609, 79-6748
Rapp, F., 79-7011
Raska, K., 79-7047
Rasmuson, A., 79-6895
Rasmuson, B., 79-6895
Raynaud, J. P., 79-6857
Recher, G., 79-6909
Recht, K. A., 79-6920
Reeves, B. R., 79-7107
Regan, J. D., 79-6890
Reilly, C. A., 79-6975
Reimer, R. R., 79-7084, 79-7086
Rein, R., 79-6743
Resnick, G., 79-7170
Rettienmier, C. W., 79-6948
Reuber, M. D., 79-6782
Reutlinger, A. H., 79-6735
Reynolds, F. H., 79-6635
Reznik-Schuller, H., 79-6725
Rhie, F. H., 79-6901
Riccardi, C., 79-7075
Riccardi, V. M., 79-7126
Ricci, C. A., 79-7173
Rice, J. M., 79-6602, 79-6716
79-6865
Richardson, D. P., 79-6694
Richard, N., 79-6933
Ridway, J. C., 79-7074
Rifkin, D. B., 79-6797
Riley, S. C., 79-6935
Ripley, S., 79-6927
Ripsey, R. M., 79-6731, 79-6816
Risser, R., 79-6974
Riverson, A., 79-6611
Robboy, S. J., 79-7171, 79-7174
Robert-Gero, M., 79-6939
Roberts, J. D., 79-6873
Robertson, D. L., 79-7054
Robinson, H. L., 79-6926
79-6927
Rocheffort, H., 79-6858
Rockus, G., 79-6975
Rodrigues, D., 79-7070
Rodriguez, L. V., 79-7122
Roessner, A., 79-7115
Rogers, M. J., 79-6991
Rohlfing, M. B., 79-7114
Rohrschneider, L. R., 79-6937
Roller, P. P., 79-6865
Rommens, C., 79-6928
Romson, J. R., 79-6807
Rose, J. S., 79-7162
Rosen, P., 79-6903
Rosen, T., 79-6738, 79-7103
Rosenberg, R. N., 79-7191
Rosenstrauss, M., 79-7079
Rosner, F., 79-7105
Rossi, L., 79-6714
Roth, D., 79-6666
Roussel, M., 79-6928
Rowe, W. P., 79-7053
Rowland, J., 79-6839
Ruckert, K., 79-6727
Ruddali, G., 79-6667
Ruddle, F. H., 79-7186
Rudolph, M., 79-7037, 79-7039
Ruiz, R., 79-7018
Runge, R., 79-6728
Rupert, C. S., 79-6621
Rushonik, S. I., 79-6924
Russell, D. H., 79-6843
Russfield, A. B., 79-6826
Rustia, M., 79-6703, 79-6850
Ryan, J. L., 79-6923
Ryan, W., 79-6829, 79-6839
Rymo, L., 79-7016
Saad, A. A., 79-7146
Sabharwal, P. S., 79-6898
Sabio, H., 79-6918
Sachs, L., 79-6794
Sacker, L. S., 79-7107
Sacks, S. T., 79-7178
Sakakibara, K., 79-6649
Sakamoto, A., 79-7140
Sakamoto, G., 79-7140
Salazar, F. H., 79-6926
Salzberg, S., 79-6985
Samaratunga, I., 79-7107
Sandberg, A. A., 79-7108
Sanford, K. K., 79-6894
Sankowski, A., 79-6832
Santoni, A., 79-7075
Sarma, D. S., 79-6779
Sato, G., 79-7200
Sato, S., 79-6796
Satterfield, L. C., 79-6674
Sauer, G., 79-7003
Saule, S., 79-6928
Savolainen, H., 79-6704
Sawicki, J., 79-6832
Schaad, J. W., 79-7169
Schafer, P. W., 79-6834
Schafer, W., 79-7001
Schaller, J. P., 79-6999
Scheib, V., 79-6770
Schenley, C. K., 79-6812
Scherneck, S., 79-7037, 79-7039
Schlake, W., 79-7129
Schochetman, G., 79-6971
Schott, D., 79-6770
Schreck, R. R., 79-6686
Schultz, E., 79-6805
Schumacher, M. J., 79-7076
Schut, H. A., 79-6681
Schwartz, R., 79-7093
Schweinsberg, F., 79-6742
Schwetz, B. A., 79-6677
Scott, K. F., 79-6843
Scott, J., 79-7168
Scribner, J. D., 79-6848
Scribner, N. K., 79-6848
Scully, R. E., 79-7174
Seemayer, N., 79-6617
Sega, M. W., 79-6812
Seidel, H. J., 79-6976
Seidman, I., 79-6666
Selkirk, J. K., 79-6837
Sell, S., 79-6787
Selvin, S., 79-7178
Senior, A., 79-6927
Seshadri, M., 79-7083
Sevc, J., 79-6910
Shaw, A., 79-6918
Shaw, J. E., 79-7017
Shellabarger, C. J., 79-6847
Shelley, E., 79-7184
Sherwin, S. A., 79-7057
Shevchenko, N. I., 79-7128
Shevliagin, V. Ia., 79-6940
79-7020
Shifrine, M., 79-7118
Shillito, E. J., 79-6641
Shimakage, M. I., 79-6947
Shimaoka, K., 79-7166
Shimm, D. S., 79-7114
Shimojo, H., 79-7048
Shinozuka, H., 79-6683
Shirai, A., 79-6776
Shirasu, Y., 79-6736, 79-6768
Shiroki, K., 79-7048
Shoji, M., 79-6796
Shoyab, M., 79-6803
Shubik, P., 79-6714, 79-6850
79-6868
Shurtz, R., 79-6985
Shvydko, N. S., 79-6924
Sieber, S. M., 79-6790
Siegler, E. L., 79-7079
Silverman, S., 79-6641

- Simeckova, B., 79-7138
Sims, P., 79-6808
Singer, G. M., 79-6745
Singer, S. S., 79-6745
Sinha, Y. N., 79-7198
Slaga, T. J., 79-6800, 79-6807
79-6813, 79-6815, 79-6827
Slamenova, D., 79-6697
Sly, D. L., 79-6716
Smiley, J. R., 79-7046
Smirnowa, E. A., 79-7119
Smith, A. C., 79-6666
Smith, A. E., 79-7034
Smith, B. L., 79-7187
Smith, C. C., 79-7009
Smith, D. M., 79-6921
Smith, D. P., 79-6890
Smith, E. J., 79-7068
Smith, E. M., 79-6640
Smith, G. C., 79-7005
Smith, K. C., 79-6622
Smith, M. C., 79-7017
Smith, R., 79-7034
Smolec, J. M., 79-6997
Snell, K., 79-6724
Snyder, R., 79-6997
Snyderman, R., 79-7095
Socher, S. H., 79-6963, 79-6969
Soeda, E., 79-7024
Sohier, R., 79-7013
Sokal, J. E., 79-7108
Solberg, L. A., 79-7143
79-7144
Sorrentino, F., 79-6615
Soto, E., 79-6822, 79-6826
Soullier, B. K., 79-6860
Sowden, J. M., 79-6806
Spadari, S., 79-6623
Spangler, W. L., 79-7118
Spelt, C. E., 79-6691
Spriggs, D. R., 79-6993
Spynu, K. I., 79-7007
Stavraky, K. M., 79-7156
Stehelin, D., 79-6928
Steimer, K. S., 79-6949
Steinheider, G., 79-6976
Steinitz, M., 79-7015
Steinitz, R., 79-7183
Stemmerman, G., 79-7149
Stenback, F., 79-6839, 79-6885
Stenback, W. A., 79-6915
Stephenson, J. R., 79-6635
Sternson, L. A., 79-6734
Stevens, R. H., 79-6916
79-7091
Stich, H. F., 79-6604
Stirling, G., 79-7146
Stock, R. J., 79-6913
Stockert, E., 79-7097
Stockert, R. J., 79-6684
Stoewsand, G. S., 79-6787
Stohrer, R., 79-6941
Stoltzfus, C. M., 79-6954
Stone, H. B., 79-6907
Stone, J. P., 79-6847
Stone, M. R., 79-6959
Strand, M., 79-6992
Sugahara, T., 79-6893
Sugano, H., 79-7140
Sugimura, T., 79-6690, 79-6737
79-6776, 79-6796, 79-6844
Sugiyama, F., 79-6768
Sula, J., 79-6633
Sullivan, M. F., 79-6923
Summers, J., 79-6997
Sundaram, K., 79-7083
Sutherland, B. M., 79-6626
79-6874
Suzuki, E., 79-6732
Suzuki, K., 79-6668
Suzuki, M., 79-6816
Suzuki, S., 79-6987
Svoboda, J., 79-6946
Swenberg, J. A., 79-6608
79-6619
Swenson, D. H., 79-6712
Syrjanen, K. J., 79-7062
Tabuchi, K., 79-7121
Tachibana, T., 79-7066, 79-7092
Tadokoro, T., 79-7131
Takahashi, M., 79-6728
Takahashi, S., 79-6683
Takaki, R., 79-6649, 79-6870
Takamori, Y., 79-6966
Takasugi, N., 79-6853
Takayama, S., 79-6737
Takemoto, K. K., 79-7032
Takizawa, S., 79-7131
Talalaeva, A. F., 79-7007
Tam, M., 79-6959
Tan Hayden, M., 79-6860
Tanaka, A., 79-6707
Tanaka, K., 79-7120
Tanaka, M., 79-6737
Tanaka, T., 79-7004, 79-7097
Tanimura, A., 79-6706
Tannenbaum, S. R., 79-6693
Tarone, G., 79-6950
Tataryn, D. N., 79-7093
Tatematsu, M., 79-6687, 79-6731
79-6816
Taylor, G. M., 79-7074
Teel, R. W., 79-6830
Teja, K., 79-6918
Temin, H. M., 79-6956
Tempete, C., 79-6939
Terada, M., 79-6844
Teresky, A. K., 79-7079
Terwindt, E., 79-6989
Thach, R. E., 79-7053, 79-7054
Theofilopoulos, A. N., 79-7085
Thiel, H., 79-6770
Thilly, W. G., 79-6700
Thomas, B. S., 79-7150
Thomas, D. B., 79-7181
Thomas, J., 79-6910
Thomas, P. E., 79-6684
Thomas, R. G., 79-6921
Thomine, J. M., 79-6908
Thompson, H. J., 79-6708
Thomson, D. M., 79-7093
Thorel, J. B., 79-6908
Thorgeirsson, S. S., 79-6681
Thorn, R. M., 79-6878
Thornby, J. I., 79-6888
Tick, N., 79-7079
Tiilikainen, A., 79-6650
Ting, C. C., 79-7070
Ting, R. C., 79-7070
Todani, T., 79-7121
Todaro, G. J., 79-7057
Tomaszewski, J. E., 79-6804
Tomatis, L., 79-6618
Tomazzoli, L., 79-6909
Tompia, A., 79-6829
Tong, D., 79-7150
Topping, D. C., 79-6802, 79-6814
Torjussen, W., 79-7143, 79-7144
79-7145
Toussaint, G., 79-6722
Toyoshima, K., 79-6947
Trentin, J. J., 79-6915, 79-7059
Tress, E., 79-6958
Trump, B. F., 79-6689, 79-6834
Tsai, S., 79-7127
Tsuda, H., 79-6779
Tsujimura, T., 79-7131
Tu, S. M., 79-7141
Turc, C., 79-6866
Turcot-Lemay, L., 79-6857
Turek, F. W., 79-7137
Turner, N., 79-7011
Tuscany, R., 79-6910
Uchino, H., 79-6706
Uehara, M., 79-7030
Ueo, H., 79-6649
Ugenas, A. J., 79-7173
Umanskii, Iu. A., 79-7072
Urbach, F., 79-6625, 79-6642
79-6884, 79-6889
Urist, M. R., 79-7117
Ushio, K., 79-6917
Uszynski, H., 79-6832
Utsumi, H., 79-6871
Utsunomiya, J., 79-7149
Utsunomiya, T., 79-7131
Valladares, Y., 79-7051
van de Ven, W. J., 79-6635
Van den Berghe, H., 79-7106
van der Ploeg, L., 79-6965
van der Putten, H., 79-6989
Van Dongen, C. G., 79-6822
van Duijn, L., 79-6965
Van Duuren, B. L., 79-6664, 79-6666
Van, J., 79-6818
van Rensburg, S. J., 79-7182
van Went, G. F., 79-6781
Vana, J., 79-6855
Vanag, K. A., 79-7007
Vandenbark, A. A., 79-7086
VanderLaan, W. P., 79-7198
Varakis, J. N., 79-7033
Variakojis, D., 79-7111
Varmus, H. E., 79-6961
Varshavsky-Rose, F., 79-6841
Vasilenko, I. V., 79-7128
Verbi, W., 79-7107
Verma, A. K., 79-6800
Vesselinovitch, S. D., 79-6609
79-6748
Vetrova, E. P., 79-7072
Vetto, R. M., 79-7086
Villani, G., 79-6623
Virtanen, A., 79-7045
Viskochil, D. H., 79-7194
Vlahakis, G., 79-7198
Vogel, F., 79-7037
von Kirchbach, A., 79-6929
Vorozhtsova, L. N., 79-6924
Voskoboinik, A. D., 79-7020
Vulterin, K., 79-7195
Wade, C. E., 79-6677
Wagner, S. L., 79-6644
Wahlte, H., 79-7037, 79-7039
Wahrendorf, J., 79-6603
Wakabayashi, Y., 79-6732
Walker, A. R., 79-7175
Walker, E. A., 79-6722
Walzak, M. P., 79-7132
Wang, D. Y., 79-7149, 79-7150
Wang, L. H., 79-6943
Wang, T. V., 79-6859
Warfel, K. A., 79-7124
Warzok, R., 79-7119
Watanabe, Y., 79-7121
Waters, R., 79-6890
Weber, G., 79-7196
Weber, J., 79-7043
Weeks, C. E., 79-6815
Weh, H. J., 79-7153
Weichselbaum, R. R., 79-7102
Weickmann, F., 79-7037, 79-7039
Weinberg, R. A., 79-6982
Weinstein, I. B., 79-6799
79-6801
Wells, R. D., 79-7026
Welsch, C. W., 79-6818
Werner, B. G., 79-6997
Werner, M., 79-7134
West, S. D., 79-6729
Westenbrink, F., 79-6973
Whitaker-Dowling, P. A.
79-6994
White, D. F., 79-7155
Whitmore, A. C., 79-6942
Wiebel, F. J., 79-6837
Wiener, F., 79-6967
Williams, G. M., 79-6688
Willingham, M. C., 79-6932
Wilson, F. D., 79-7118
Wilson, P. S., 79-6860
Wilson, R., 79-6868
Wilson, R. B., 79-7125
Winkelmann, R. K., 79-7158
Wintrobe, M. M., 79-7164
Wishnok, J. S., 79-6694
Witschi, H., 79-6699
Witter, R. L., 79-7068
Wivel, N., 79-7070
Wojciechowska, M., 79-6832
Wolman, S. R., 79-6670
Wozniak, L., 79-6663
Wronkowski, Z., 79-7183
Wu, M., 79-7022, 79-7027
Wu, R., 79-7031
Wu, Y. H., 79-6990
Wynder, E., 79-7157
Wynder, E. L., 79-6611, 79-7175
Yagi, H., 79-6861
Yakimenko, L. V., 79-7072
Yam, A., 79-6684
Yamada, T., 79-6706
Yamagami, H., 79-6649, 79-6870
Yamaguchi, M., 79-6834
Yamaha, T., 79-6707
Yamamoto, M., 79-6706
Yamamoto, T., 79-6978
Yamanaka, H., 79-6776
Yamashiro, S., 79-6845
Yamashita, N., 79-7139
Yang, C. S., 79-7141
Yang, J. A., 79-6786
Yang, R. C., 79-7031
Yano, K., 79-6867
Yarita, T., 79-6710
Yerganian, G., 79-6672
Yoshida, M., 79-6771
Yoshikawa, K., 79-6706
Younghusband, H. B., 79-7044
Yuhas, J. M., 79-6897
Zaharopoulos, P., 79-7130
Zahn, R. K., 79-7006
Zajdela, F., 79-6876
Zakov, Z. N., 79-7102
Zankl, H., 79-7099
Zannoni, V. G., 79-6746
Zarrabi, M. H., 79-7105
Zellmann, H. E., 79-6901
Zhdanov, V. M., 79-7058
Zimmermann, W., 79-7037
79-7039
Zoltowska, A., 79-6988
Zu Rhein, G. M., 79-7033
Zuberi, S. J., 79-6791

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Subject Index

Abdominal Neoplasms

- Angiosarcoma
 - Azobenzene, 79-6766
- Fibrosarcoma
 - Azobenzene, 79-6766
- Sarcoma, Osteogenic
 - Azobenzene, 79-6766

Abnormalities

- Hyperthermia
 - Hamster, 79-6900
- Retinol
 - Hamster, 79-6900
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Vagina, Cervix, 79-7174

Acetaldehyde

- Anemia, Aplastic
 - Sister-Chromatid Exchange, 79-6661
- Benzo(a)pyrene
 - Co-carcinogenic Effect, 79-6678
- Diethylamine, *N*-Nitroso-
 - Co-carcinogenic Effect, 79-6678

Acetaldehyde, Chloro-

- Ether, Bis(2-chloroethyl)-
 - Hepatocarcinogenesis, 79-6739

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

- Acetohydroxamic Acid, *N*-4-Biphenyl-, Potassium Salt
 - DNA Substitution Products, 79-6680
- Caffeine
 - Cell Transformation, Neoplastic 79-6891
- DNA
 - Nucleic Acid Denaturation, 79-6691
- DNA Repair
 - Fibroblasts, 79-6873
 - Nucleotides, 79-6873
- Guanosine, 2'-Deoxy-
 - Endonucleases, 79-6691
- RNA Adducts
 - Liver, Rat, 79-6848
- Ultraviolet Rays
 - Cell Transformation, Neoplastic 79-6891
- Xeroderma Pigmentosum
 - DNA Repair, 79-6873

Acetamide, *N*-(4-(1,2-Dihydroxy-2-phenylethyl)phenyl)-4-Stilbenamine, *N,N*-Dimethyl-RNA Adducts, 79-6848

Acetamide, *N*-Fluoren-2-yl-

- Cholanthrene, 3-Methyl-
 - Microsomes, Liver, 79-6685
- Chromatids
 - Bone Marrow, 79-6686
 - Liver Regeneration, 79-6686
- Chromosome Aberrations
 - Mutagenic Metabolite, 79-6744
- Glucosephosphate Dehydrogenase
 - Enzymatic Activity, 79-6682
- Hepatoma
 - Chromosomal Proteins, Non-Histone 79-7122
 - Hyperplasia, 79-7123
 - Precancerous Conditions, 79-7123
- Hyperplasia
 - Barbituric Acid, 5-Ethyl-5-phenyl- 79-6687
 - 5,6-Benzoflavone, 79-6687
 - Cholanthrene, 3-Methyl-, 79-6687
 - Kanechlor 500, 79-6687
- Liver Neoplasms
 - Hyperplasia, 79-6684, 79-6688
 - 2,4-Oxazolidinedione, 3-(3,5-Dichlorophenyl)-5,5-dimethyl- 79-6687
 - Precancerous Conditions, 79-6687
 - Selenium, 79-6685
 - Serine, Diazoacetate (Ester), 79-6683

Acetamide, *N*-Fluoren-2-yl- (cont'd)

- Phosphoglucanate Dehydrogenase
 - Enzymatic Activity, 79-6682
- Selenium
 - Metabolism, 79-6685
 - Microsomes, Liver, 79-6685
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Ames Test, 79-6679

Acetanilide, 4'-(*p*-Fluorophenyl)-

- Adenocarcinoma
 - Acetic Acid, Lead Salt, 79-6689
- Cytochrome P-450
 - Liver, Rat, 79-6689
- Hepatoma
 - Acetic Acid, Lead Salt, 79-6689
- Kidney Neoplasms
 - Adenocarcinoma, 79-6689

Acetanilide, 4'-Hydroxy-

- Carcinogenic Metabolite
 - Liver, Review, 79-6616

Acetic Acid, Lead Salt

- Adenocarcinoma
 - Acetanilide, 4'-(*p*-Fluorophenyl)- 79-6689
- Calcium
 - Chromosome Aberrations, 79-6646
- Hepatoma
 - Acetanilide, 4'-(*p*-Fluorophenyl)- 79-6689
- Kidney Neoplasms
 - Adenocarcinoma, 79-6689

Acetic Acid, Methylnitrosaminomethyl Ester

- Esterases
 - Metabolism, Rat, 79-6865
- Guanine, 7-Methyl-
 - Organ Specificity, 79-6865
- Phosphorofluoridic Acid, Bis(1-methylethyl) Ester
 - DNA, Alkylation, 79-6865
- Purine, 2-Amino-6-methoxy-
 - Organ Specificity, 79-6865

Acetic Acid, Thiodi-

- Ether, Bis(2-chloroethyl)-
 - Urinary Metabolites, 79-6739

Acetic Acid, (2,4,5-Trichlorophenoxy)-

- Carcinogenic Potential
 - Dose-Response Study, Rat, 79-6677
- Dibenzo-*p*-dioxin, 2,7-Dichloro-
 - Environmental Hazard, 79-6774
- Kidney Diseases
 - Toxicity, Rat, 79-6677
- Porphyrins
 - Metabolism, 79-6677

Acetohexamide

- see Urea, 1-((*p*-Acetylphenyl)sulfonyl)-3-cyclohexyl-

Acetohydroxamic Acid, *N*-4-Biphenyl-, Potassium Salt

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - DNA Substitution Products, 79-6680

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

- Acylesterase
 - Small Intestine, Rat, 79-6681
- Acyltransferases
 - Small Intestine, Rat, 79-6681
- Ames Test
 - Enzyme Activation, 79-6681
- Ascorbic Acid
 - Mutagenic Activity, 79-6681
- DNA Replication
 - Liver Regeneration, 79-6864
- Phosphoric Acid, Tris(*p*-nitrophenyl) Ester
 - Mutagenic Activity, 79-6681

Acetohydroxamic Acid, *N*-Fluoren-2-yl- (cont'd)

- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Ames Test, 79-6679

Acetohydroxamic Acid, *N*-Fluoren-3-yl-

- Selenium
 - Metabolism, 79-6685

p-Acetophenetidine

- Urologic Neoplasms
 - Nephritis, Interstitial, 79-6615

Acetophenone

- Phenethylamine, *N*-Methyl-*N*-nitroso-
 - Microsomes, Liver, 79-6742

Acetylcholinesterase

- Virus, Rous Sarcoma
 - Cell Cycle Kinetics, 79-6945

Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-

- Adrenal Gland Neoplasms
 - Pheochromocytoma, 79-6690
- Esophageal Neoplasms
 - Dose-Response Study, Hamster 79-6690
- Stomach Neoplasms
 - Carcinoma, Epidermoid, 79-6690

Actin

- Phorbol 12,13-Didecanoate
 - Fibroblasts, 79-6797
- RNA, Messenger
 - Poly A, 79-7191
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Fibroblasts, 79-6797
 - RNA Replication, 79-6797

Actinomycin D

- L Cells
 - Polyribosomes, 79-7192
- MSH
 - Tyrosinase, 79-7194
- Plasmacytoma
 - Polyribosomes, 79-7192

Acylesterase

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Small Intestine, Rat, 79-6681

Acyltransferases

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Small Intestine, Rat, 79-6681

Adenocarcinoma

- Acetanilide, 4'-(*p*-Fluorophenyl)-
 - Acetic Acid, Lead Salt, 79-6689
- Amidophosphoribosyltransferase
 - Adenosine Monophosphate, 79-7196
- Benz(a)anthracene, 7,12-Dimethyl-
 - Corn Oil, 79-6817
 - Dietary Fats, 79-6817
- Bile Duct Neoplasms
 - Cysts, 79-7121
- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)- 79-6733
- Cervix Neoplasms
 - Epidemiology, 79-7136
- Cholesterol
 - Hydroxymethylglutaryl CoA Reductases, 79-7197
 - Pentanoic Acid, 3,5-Dihydroxy-3-methyl-, 79-7197
 - Squalene, 79-7197
- Colonic Neoplasms
 - Radiation, Ionizing, 79-6918
 - Rectocolitis, 79-6919
 - Urinary Diversion, 79-6920
 - Virus, Cytomegalo, 79-7012
- Endometriosis
 - Case Report, 79-6854
- Gastrointestinal Neoplasms
 - Genetics, Rat, 79-7131

Adenocarcinoma (cont'd)
 Peutz-Jeghers Syndrome, 79-7130
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Cyclophosphamide, 79-6866
 Hodgkin's Disease
 Immunologic Deficiency Syndromes
 79-7088
 Intestinal Neoplasms
 Histological Study, Rat, 79-6673
 Hydrazine, 1,2-Dimethyl-, 79-6674
 Immune Serums, 79-6916
 Methane, Azoxy-, 79-6860
 Precancerous Conditions, 79-6673
 Radiation, Ionizing, 79-6916, 79-6917
 Kidney Neoplasms
 Acetanilide, 4'-(*p*-Fluorophenyl)-
 79-6689
 Acetic Acid, Lead Salt, 79-6689
 Amidophosphoribosyltransferase
 79-7196
 Cholesterol, 79-7197
 Genetics, 79-7127
 2-Imidazolidinone, 1-(5-Nitro-2-
 thiazolyl)-, 79-6868
 Sertoli Cell Tumor, 79-6792
 Virus, Herpes Lucke, 79-7169
 Lung Neoplasms
 2-Imidazolidinethione, *N*-Nitroso-
 79-6736
 Neoplasm Metastasis, 79-6728
 Polonium, 79-6922
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6667, 79-6817
 Carbamic Acid, Diethyldithio-, 2-
 Chloroallyl Ester, 79-6702
 Methanesulfonic Acid, Ethyl Ester
 79-6649
 Sialyltransferase, 79-6817
 4,4'-Stilbenediol, α,α' -Diethyl-
 79-6847
p-Toluamide, *N*-Isopropyl- α -(2-
 methylhydrazino)-, 79-6750
 Neoplasms, Multiple Primary
 Hodgkin's Disease, 79-7088
 Nose Neoplasms
 Transplacental Carcinogenesis
 79-6725
 Ovarian Neoplasms
 Endometriosis, 79-7133
 Genetics, 79-7133
 Pancreatic Neoplasms
 Dipropylamine, 2,2'-Dioxo-*N*-nitroso-
 79-6728
 Prostatic Neoplasms
 Reverse Transcriptase, 79-7052
 Respiratory Tract Neoplasms
 1*H*-Azepine, Hexahydro-1-nitroso-
 79-6612
 Azocine, Octahydro-1-nitroso-
 79-6612
 Benzo(a)pyrene, 79-6678
 Salivary Gland Neoplasms
 Virus, Herpes Simplex 1, 79-7007
 Stomach Neoplasms
 Gastrectomy, 79-7129
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 79-6866
 NADH, NADPH Oxidoreductases
 79-7128
 Neoplasm Transplantation, 79-6866
 Thyroid Neoplasms
 Carbamic Acid, Diethyldithio-, 2-
 Chloroallyl Ester, 79-6702
 Radiation, Ionizing, 79-7140
 Urea, 1,1,3-Trimethyl-2-thio-, 79-6711
 Tracheal Neoplasms
 Precancerous Conditions, 79-6710
 Urea, Methyl Nitroso-, 79-6708
 Transplantation, Homologous
 Neoplasm Metastasis, 79-6728
 Uterine Neoplasms
 Enovid, 79-6854
 Estrogens, 79-7173
 Histological Study, 79-7171
 Pregn-4-ene-3,20-dione, 17-(Acetyloxy)-
 6 α -methyl-, 79-6854

Adenocarcinoma (cont'd)
p-Toluamide, *N*-Isopropyl- α -(2-
 methylhydrazino)-, 79-6750
 Virus, Cytomegalo
 Cells, Cultured, 79-7012
 Virus, Herpes Lucke
 Epidemiology, 79-7169
 Virus, Herpes Simplex 1
 Carcinogenic Activity, Mouse, 79-7007
 Virus, Murine Mammary Tumor
 Phosphoproteins, 79-6962
Adenocarcinoma, Papillary
 Lung Neoplasms
 Virus, SV40, 79-7041
 Ovarian Neoplasms
 Endometriosis, 79-7133
Adenofibroma
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6667
 Carcinogenic Potential, 79-6752
 Radiation, Ionizing, 79-6847
 4,4'-Stilbenediol, α,α' -Diethyl-
 79-6847
 Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-
 79-6713
 Skin Neoplasms
 Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-
 79-6713
Adenoma
 Adrenal Gland Neoplasms
 Phosphorothioic Acid, *O,O*-Diethyl *O*-
 (*p*-Nitrophenyl) Ester, 79-6765
 Eye Neoplasms
 Benzenamine, *N*-Hydroxy-*N*-nitroso-,
 Ammonium Salt, 79-6754
 Tellurium, Tetrakis(diethyldithiocar-
 bamato)-, 79-6658
 Gynecologic Neoplasms
 1,5-Naphthalenediamine, 79-6772
 Hepatoma
 1,5-Naphthalenediamine, 79-6772
 Intestinal Neoplasms
 Hydrazine, 1,2-Dimethyl-, 79-6673
 79-6674
 Kidney Neoplasms
 Dimethylamine, *N*-Nitroso-, 79-6863
 2-Imidazolidinone, 1-(5-Nitro-2-
 thiazolyl)-, 79-6868
 Liver Neoplasms
 Contraceptives, Oral, 79-6855
 Ethane, 1,1-Dichloro-2,2-bis(*p*-
 ethylphenyl)-, 79-6665
 Phenol, 2,4,6-Trichloro-, 79-6747
 Lung Neoplasms
 Carbamic Acid, Ethyl Ester, 79-6699
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6753
 Diphenylamine, *N*-Nitroso-, 79-6730
 Lactate Dehydrogenase, 79-6698
 1,5-Naphthalenediamine, 79-6772
 Phthalic Anhydride, 79-6762
 Terephthalic Acid, Dimethyl Ester
 79-6749
p-Toluamide, *N*-Isopropyl- α -(2-
 methylhydrazino)-, 79-6750
 Urea, Ethyl Nitroso-, 79-6714
 Virus, SV40, 79-7041
 Mammary Neoplasms, Experimental
 Mucopolysaccharides, 79-7199
 Pituitary Neoplasms
 Anthraquinone, 1-Amino-2-methyl-
 79-6792
 Respiratory Tract Neoplasms
 Benzo(a)pyrene, 79-6678
 Diethylamine, *N*-Nitroso-, 79-6678
 Thyroid Neoplasms
 1,5-Naphthalenediamine, 79-6772
 Phosphamidon, 79-6655
Adenoma, Chromophobe
 Pituitary Neoplasms
 Radiation Effects, 79-6902
Adenosine
 Carcinogen, Chemical

Adenosine (cont'd)
 Benzoylation, 79-6740
Adenosine Cyclic 3',5' Monophosphate
 Isoproterenol
 Mezeirin, 79-6800
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6800
 Melanoma
 MSH, 79-7194
Adenosine, 3'-Deoxy-
 Virus, Herpes Simplex 1
 Ribonucleotides, 79-7006
Adenosine Monophosphate
 Adenocarcinoma
 Amidophosphoribosyltransferase
 79-7196
Adrenal Gland Neoplasms
 Adenoma
 Phosphorothioic Acid, *O,O*-Diethyl *O*-
 (*p*-Nitrophenyl) Ester, 79-6765
 Carcinoma
 Phosphorothioic Acid, *O,O*-Diethyl *O*-
 (*p*-Nitrophenyl) Ester, 79-6765
 Cyanamide, Calcium Salt
 Dose-Response Study, 79-6647
 Ganglioneuroma
 Benzenamine, *N*-Hydroxy-*N*-nitroso-,
 Ammonium Salt, 79-6754
 Hyperplasia
 Pentadecane, 2,6,10,14-Tetramethyl-
 79-6672
 Petroleum, 79-6672
 Pheochromocytoma
 Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-
 furyl)-, 79-6690
 α -Tolidine, 5-Chloro-, 79-6751
 Phosphorothioic Acid, *O,O*-Diethyl *O*-(*p*-
 Nitrophenyl) Ester
 Dose-Response Study, 79-6765
Adriamycin
 Retinol
 Ames Test, 79-6842
Aflatoxin B1
 Alpha Fetoproteins
 Serum Levels, 79-6787
 Bladder Neoplasms
 Papilloma, 79-6790
 Cauliflower
 Carcinogenic Activity, 79-6787
 DNA Adducts
 Cells, Cultured, Lung, 79-6859
 Gallbladder Neoplasms
 Carcinoma, 79-6790
 Hemangioendothelioma
 Pancreatic Neoplasms, 79-6790
 Hepatoma
 Carcinogenic Activity, Monkey
 79-6790
 Liver Neoplasms
 Amaranth, 79-6791
 Mixed Function Oxidases
 Liver, Rat, 79-6787
 Orotic Acid
 Metabolism, Gerbil, 79-6788
 Pancreatic Neoplasms
 Carcinoma, 79-6790
 Perinatal Carcinogenesis
 Mouse, Review, 79-6609
 Sarcoma, Osteogenic
 Carcinogenic Activity, Monkey
 79-6790
**Aflatoxin B1, 2,3-Dihydro-3-(*N*-guanyl)-3-
 hydroxy-**
 DNA Adducts
 Cells, Cultured, Lung, 79-6859
Aflatoxin G1
 Immune Serums
 Antibody Specificity, 79-6789
Aflatoxin M1
 Immune Serums
 Antibodies, 79-6789

Aflatoxin M1 (cont'd)
Antibody Specificity, 79-6789

Air Pollutants
Oncogenic Viruses
Co-carcinogenic Effect, Review
79-6617

Air Pollution
Hodgkin's Disease
Solvents, 79-7165
Laryngeal Neoplasms
Solvents, 79-7165
Leukemia
Solvents, 79-7165
Lymphoma
2-Butanone, 79-7165
2-Pentanone, 4-Methyl-, 79-7165
Pancreatic Neoplasms
Solvents, 79-7165
Sarcoma, Reticulum Cell
Solvents, 79-7165

Alanine, 3-(β -Bis(2-chloroethyl)amino)phenyl)-
Leukemia
Epidemiology, 79-7155

Alanine, 3-((Carboxymethyl)thio)-
Ether, Bis(2-chloroethyl)-
Urinary Metabolites, 79-6739

Alanine, 3-(3,4-Dihydroxyphenyl)-
Melanoma
Melanosomes, Incorporation, 79-7195

Aldicarb
Cell Transformation, Neoplastic
N-Nitroso Derivatives, 79-6812
Dose-Response Study
Carcinogenic Potential, 79-6780

Alkaline Phosphatase
Bladder Neoplasms
Precancerous Conditions, Rat, 79-6733

Allyl Chloride
see Propene, 3-Chloro-

Alpha Fetoproteins
Aflatoxin B1
Serum Levels, 79-6787
Hepatoma
RNA, Messenger, 79-7094
RNA, Messenger
Isolation and Characterization
79-7094

Alpha Particles
Lung Neoplasms
Microspheres, 79-6921

Amaranth
Liver Neoplasms
Aflatoxin B1, 79-6791

Ameloblastoma
Jaw Neoplasms
Urea, Ethyl Nitroso-, 79-6715

Ames Test
Acetamide, N-Fluoren-2-yl-
4,4'-Stilbenediol, α,α' -Diethyl-
79-6679
Acetohydroxamic Acid, N-Fluoren-2-yl-
Enzyme Activation, 79-6681
4,4'-Stilbenediol, α,α' -Diethyl-
79-6679
Adriamycin
Retinol, 79-6842
Aniline, 4,4'-Sulfonyldi-
Mutagenic Activity, Review, 79-6613
4-Biphenylamine
Bile, 79-6768
4-Biphenylamine, 3,2'-Dimethyl-
Bile, 79-6768
1-Butanol, (4-Butylnitrosamino)-
 α -Acetoxy Derivatives, 79-6732
Carbamic Acid, N-Methyl-N-nitroso-,
Ethyl Ester
Mutagenic Activity, 79-6700

Ames Test (cont'd)
Fluoren-2-amine
Microsomes, Liver, 79-6842
Retinol, 79-6842
Heliotrine
S9 Fraction, 79-6776
Hydrazine, 1,2-Dimethyl-
Bile, 79-6768
Lasiocarpine
Pyrrolizidine Alkaloids, 79-6776
S9 Fraction, 79-6776
Methane, Azoxy-
Bile, 79-6768
Methanesulfonic Acid, Butyl Ester
Azaguanine Resistance, 79-6700
Methanol, (Methyl-ONN-azoxy)-, Ace-
tate (Ester)
Bile, 79-6768
Methylamine, N-Nitroso-
 α -Acetoxy Derivatives, 79-6732
Nitrous Acid
Gastric Juice, 79-6692
2-Oxetanone
Mutagenic Activity, 79-6700
Urea, 1,3-Dimethyl-1-nitroso-
Aryl Derivatives, 79-6867
Urea, Methyl Nitroso-
Aryl Derivatives, 79-6867

Amino Acids
Virus, Rauscher Murine Leukemia
Binding Sites, 79-6992
Phosphoproteins, 79-6990

Ammonium, 2-Chloroethyltrimethyl-, Chloride
Carcinogenic Potential
Dose-Response Study, 79-6676

Amphetamines
Hodgkin's Disease
Risk Factors, 79-7160

Amprolium
Chromosome Aberrations
Micronucleus Test, 79-6735

Amyloidosis
Sarcoma Kaposi's
Case Report, 79-7114

Androgens
Diet
Metabolism, Men, 79-7175

Androst-4-ene-3,17-dione
Breast Neoplasms
Plasma Levels, 79-7150

5 α -Androstan-3-one, 17 β -Hydroxy-
Vaginal Neoplasms
Precancerous Conditions, 79-6853

Anemia
Virus, Friend Murine Leukemia
Virus, Helper, 79-6976

Anemia, Aplastic
Acetaldehyde
Sister-Chromatid Exchange, 79-6661
Butane, 1,2,3,4-Diepoxy-
Chromosome Aberrations, 79-6670
Ethyl Alcohol
Sister-Chromatid Exchange, 79-6661
Thorium Dioxide
Case Report, 79-6770
Ultraviolet Rays
DNA Repair, 79-6890

Anemia, Sideroblastic
Leukemia
Epidemiology, 79-7164
Precancerous Conditions, 79-7164

Angioma
Skin Neoplasms
Ultraviolet Rays, 79-6885

Angiosarcoma
Abdominal Neoplasms
Azobenzene, 79-6766

Angiosarcoma (cont'd)
Benzenamine, N-Hydroxy-N-nitroso-,
Ammonium Salt
Dose-Response Study, 79-6754
Cyanamide, Calcium Salt
Dose-Response Study, 79-6647
Dibenzo-*p*-dioxin, 2,7-Dichloro-
Carcinogenic Potential, 79-6774
Skin Neoplasms
Ultraviolet Rays, 79-6885
Splenic Neoplasms
Phosphamidon, 79-6655
 α -Toluidine, 5-Chloro-
Dose-Response Study, 79-6751
Ultraviolet Rays
Dose-Response Study, 79-6882
Virus, Herpes Simplex 2
Carcinogenic Activity, Mouse, 79-7007

Aniline, Dinitro- (Mixed Isomers)
Nitrosamines
Food Contamination, 79-6729

Aniline, 4,4'-Sulfonyldi-
Ames Test
Mutagenic Activity, Review, 79-6613
Carcinogenic Potential
Rat, Review, 79-6613

Anisole, *p*-Allyl-
Food Contamination
Carcinogenic Potential, Review
79-6614

1-Anthracenamide
Ethyl Alcohol
Emission Spectra, 79-6761
Excited States
Fluorescence, 79-6761

2-Anthracenamide
Ethyl Alcohol
Emission Spectra, 79-6761
Excited States
Fluorescence, 79-6761

Anthraquinone, 1-Amino-2-methyl-
Hepatoma
Dose-Response Study, 79-6792
Pituitary Neoplasms
Adenoma, 79-6792
Sertoli Cell Tumor
Dose-Response Study, 79-6792

Anti-Antibodies
Erythroleukemia
Virus, Moloney Murine Sarcoma
79-6988
Sarcoma
Virus, Moloney Murine Sarcoma
79-6988
Virus, Epstein-Barr
Haptens, 79-7015
Virus, Moloney Murine Sarcoma
Interferon, 79-6988

Antibodies
Aflatoxin M1
Immune Serums, 79-6789
Benzo(a)pyrene
Hemagglutination Tests, 79-6829
Mutagenic Activity, 79-6829
Leukemia, Myeloblastic
Rosette Formation, 79-7074
Leukemia, Myelocytic
Rosette Formation, 79-7074

Antibodies, Viral
Burkitt's Lymphoma
Virus, Adeno 4, 79-7013
Virus, Cytomegalo, 79-7013
Virus, Herpes Simplex 1, 79-7013
Virus, Measles, 79-7013
Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor
79-6971
Virus, Murine Leukemia
Hybrid Cells, 79-6959
Virus, Murine Mammary Tumor
Antigenic Determinants, 79-6971

Antibodies, Viral (cont'd)
Strain Difference, 79-6971

Antibody Specificity

Aflatoxin G1
Immune Serums, 79-6789
Aflatoxin M1
Immune Serums, 79-6789
Virus, AKR Murine Leukemia
Antigenic Determinants, 79-6957
Virus, Avian Sarcoma
Phosphoproteins, 79-6935
Virus, B77
Phosphoproteins, 79-6935
Virus, Moloney Murine Leukemia
Antigens, Neoplasm, 79-6987
Virus, Murine Leukemia
Antigenic Determinants, 79-6959
Viral Proteins, 79-6957

Antigen-Antibody Complex

Melanoma
IgG, 79-7085
Neoplasms, Experimental
Hybrid Cells, 79-7066
Virus, Rous Sarcoma
Immunoprecipitation, 79-6951

Antigen-Antibody Reactions

Nasopharyngeal Neoplasms
Virus, Epstein-Barr, 79-7018
Virus, Friend Murine Leukemia
Immune Serums, 79-6977
Virus, Herpes Simplex 2
Viral Proteins, 79-7009

Antigenic Determinants

Virus, AKR Murine Leukemia
Antibody Specificity, 79-6957
Virus, Avian Leukosis
DNA Polymerase, 79-6956
Virus, Avian Sarcoma
Phosphoproteins, 79-6935
Virus, C-Type RNA Tumor
Colobus polykomos, 79-7057
Virus, MC29
Virus, Helper, 79-7060
Virus, Murine C-Type Myeloma
Virus, Murine Leukemia, 79-6993
Virus, Murine Leukemia
Antibody Specificity, 79-6959
Virus, Feline Leukemia, 79-6959
Virus, Murine Mammary Tumor
Antibodies, Viral, 79-6971
Viral Proteins, 79-6964
Virus, Pheasant RNA Tumor
DNA Polymerase, 79-6956
Virus, Avian Leukosis, 79-6956
Virus, Polyoma, BK
Virus, SV40, 79-7032
Virus, Rauscher Murine Leukemia
Immunity, Cellular, 79-6991
Viral Proteins, 79-6990
Virus, Rous-Associated
Pactamycin, 79-6948
Viral Proteins, 79-6948
Virus, Rous Sarcoma
Viral Proteins, 79-6941
Virus Rescue, 79-6949
Virus, Stump-Tailed Macaque
Viral Proteins, 79-7003
Virus, Woodchuck Hepatitis
Virus, Hepatitis, 79-6997

Antigens

4,4'-Stilbenediol, α,α' -Diethyl-
Estradiol, 79-6852
Virus, Adeno 12
Cell Membrane, 79-7048

Antigens, Neoplasm

Breast Neoplasms
Leukocyte Adherence Inhibition Test
79-7093
Neoplasm Metastasis, 79-7093
Colonic Neoplasms
Leukocyte Adherence Inhibition Test
79-7093
Neoplasm Metastasis, 79-7093

Antigens, Neoplasm (cont'd)

Fibrosarcoma
Virus, Friend Murine Leukemia
79-6977
Glioblastoma Multiforme
Virus, SV40, 79-7037
Hypersensitivity, Delayed
Rosette Formation, 79-7087
Leukemia
Transplantation Immunology, 79-6878
Lung Neoplasms
Carcinoma, Epidermoid, 79-7091
Fetal Globulins, 79-7091
Lymphoma
Virus, Moloney Murine Leukemia
79-6987
Mammary Neoplasms, Experimental
Hybrid Cells, 79-7092
Melanoma
Horizontal Transmission, 79-7086
Hypersensitivity, Delayed, 79-7087
Leukocyte Adherence Inhibition Test
79-7086
Lymphocytes, 79-7087
Meningioma
Virus, SV40, 79-7039
Nephroblastoma
Immune Serums, 79-7096
Isolation and Characterization
79-7096
Ultraviolet Rays
Transplantation Immunology, 79-6879
Virus, Adeno 12
DNA, Viral, 79-7050
Immune Serums, 79-7047
Protein Kinase, 79-7047
Virus, CELO
Genes, Viral, 79-7059
Virus, Gross Murine Leukemia
Killer Cells, 79-6980
Virus, Moloney Murine Leukemia
Antibody Specificity, 79-6987
Virus, Polyoma
Cell Membrane, 79-7029
DNA, Viral, 79-7021
Nucleotide Sequence, 79-7024
Virus, Rous Sarcoma
Cell Membrane, 79-6950
Cell Transformation, Neoplastic
79-6951
Immunity, Cellular, 79-6952
Immunoprecipitation, 79-6951
Virus, SV40
Cells, Cultured, 79-7035
Deletion Mutants, 79-7036, 79-7038
Immunoprecipitation, 79-7034
Isolation and Characterization
79-7038
RNA, Messenger, 79-7034

Antigens, Viral

Carcinoma
Virus, Herpes Simplex 2, 79-7008
Fibrosarcoma
Virus, Friend Murine Leukemia
79-6977
Virus, Herpes Simplex 2, 79-7007
Hepatoma
Virus, Hepatitis, 79-7063
Lymphoma
Immunologic Technics, 79-7061
Virus, Herpes Simplex 1, 79-7007
Virus, Herpes Simplex 2, 79-7007
Virus, Moloney Murine Leukemia
79-6987
Mammary Neoplasms, Experimental
Virus, Murine Leukemia, 79-6967
Virus, Murine Mammary Tumor
79-6967, 79-6972
Virus, Abelson Murine Leukemia
Hematopoietic Stem Cells, 79-6974
Immunogenetics, 79-6974
Virus, Adeno 12
Cell Membrane, 79-7049
Cell Transformation, Neoplastic
79-7049
DNA, Viral, 79-7050

Antigens, Viral (cont'd)

Transplantation Immunology, 79-7049
Virus, D-Type RNA Tumor
Isolation and Characterization
79-7058
Virus, Gross Murine Leukemia
T-Lymphocytes, 79-6981
Neonatal Infection, 79-6981
Virus, Murine Mammary Tumor
Milk, 79-6972, 79-6973
Rabbit, Rat, 79-6973
Virus, Newcastle Disease
Immunologic Technics, 79-7061
Virus, Rous Sarcoma
Antibody Formation, 79-6952
Virus, Sendai
Immunologic Technics, 79-7061
Virus, Woodchuck Hepatitis
Australia Antigen, 79-6997

Antilymphocyte Serum

Virus, Adeno 2
T-Lymphocytes, 79-7042
Virus, Murine Sarcoma
T-Lymphocytes, 79-6960
Virus, Rous Sarcoma
T-Lymphocytes, 79-6942
Tumor Latency, 79-6942

Antipain

Virus, C-Type RNA Tumor
Radiation, Ionizing, 79-6893
Ultraviolet Rays, 79-6893
Uridine, 5-Bromo-2'-deoxy-, 79-6893
Virus Activation, 79-6893

Aroclor 1254

Hyperplasia
Epidermis, Mouse, 79-6813
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6813

Arsenic

Skin Neoplasms
Carcinoma, Basal Cell, 79-6644
Carcinoma, Epidermoid, 79-6644
Water Pollution, 79-6644

Arthritis, Adjuvant

Mycobacterium butyricum
Macrophages, 79-7081

Aryl Hydrocarbon Hydroxylases

Benz(a)anthracene, 7,12-Dimethyl-
Lung Cells, 79-6830
Benzo(a)pyrene
Lung Cells, 79-6830
Cholanthrene, 3-Methyl-
Lung Cells, 79-6830
Polycyclic Hydrocarbons
Lymphocytes, 79-6819

Asbestos

Benzo(a)pyrene
Co-carcinogenic Effect, 79-6831
Transport, Microsomes, 79-6831
Mesothelioma
Fiber Mixture, Review, 79-6639
Pulmonary Fibrosis
Histocompatibility Antigens, 79-6650
Tracheal Neoplasms
Cholanthrene, 3-Methyl-, 79-6824
79-6825

Asbestosis

Lung Neoplasms
Histocompatibility Antigens, 79-6650
Smoking, 79-6650

Ascorbic Acid

Acetohydroxamic Acid, *N*-Fluorene-2-yl-
Mutagenic Activity, 79-6681

Aspergillus nidulans

4,4'-Bipyridinium, 1,1'-Dimethyl-, Di-
chloride
Mutagenic Activity, 79-6758
Dipyrido(1,2-a:2',1'-c)pyrazinedium, 6,
7-Dihydro-

Aspergillus nidulans (cont'd)
Mutagenic Activity, 79-6758

Astrocystoma
DNA, Neoplasm
DNA-RNA Hybridization, 79-7190

Ataxia Telangiectasia
Butane, 1,2:3,4-Diepoxy-
Chromosome Aberrations, 79-6670

Australia Antigen
Hepatoma
Ultrastructural Study, 79-7063
Virus, Woodchuck Hepatitis
Antigens, Viral, 79-6997

Autoantibodies
Glomerulonephritis
Virus, Murine Leukemia, 79-7097
Sarcoma, Reticulum Cell
Virus, Murine Leukemia, 79-7097

β -Azarone
sec Benzene, 1,2,4-Trimethoxy-5-(1-propenyl)-

Azathioprine
Chromosome Aberrations
Drug Therapy, 79-6781
Lymphocytes, 79-6781

1-H-Azepine, Hexahydro-1-nitroso-
Digestive System Neoplasms
Hamster, Review, 79-6612
Respiratory Tract Neoplasms
Adenocarcinoma, 79-6612
Transplacental Carcinogenesis
Hamster, 79-6721

Azobenzene
Abdominal Neoplasms
Angiosarcoma, 79-6766
Fibrosarcoma, 79-6766
Sarcoma, Osteogenic, 79-6766
Splenic Neoplasms
Hemangiopericytoma, 79-6766

Azobenzene, 3,3',4,4'-Tetrachloro-
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6813

Azocine, Octahydro-1-nitroso-
Digestive System Neoplasms
Hamster, Review, 79-6612
Respiratory Tract Neoplasms
Adenocarcinoma, 79-6612

Bacillus subtilis
Nitrosamines
Mutagenic Activity, 79-6732

Bacterioides mullacicus
Liver Neoplasms
Mouse, 79-6643

Barbituric Acid, 5-Ethyl-5-phenyl-
Aryl Hydrocarbon Hydroxylases
Lymphocytes, 79-6819
Benzaldehyde
Metabolism, Rat, 79-6742
Benzene, Bromo-
Epoxide Metabolites, 79-6746
Hyperplasia
Acetamide, *N*-Fluoren-2-yl-, 79-6687
Phenethylamine, *N*-Methyl-*N*-nitroso-
Formaldehyde, 79-6742
Phenol, α -Bromo-
Metabolism, Liver, 79-6746
Phenol, ρ -Bromo-
Metabolism, Liver, 79-6746

Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
Intestinal Neoplasms
Co-carcinogenic Effect, 79-6675
Hydrazine, 1,2-Dimethyl-, 79-6675
Methanol, (Methyl-*ONN*-azoxy)-,
Acetate (Ester), 79-6675

Benz(a)anthracene
Aryl Hydrocarbon Hydroxylases
Lymphocytes, 79-6819

Benz(a)anthracene, 7-Bromo-methyl-12-methyl-
DNA Repair
DNA Adducts, 79-6805
L Cells
DNA Repair, 79-6805

Benz(a)anthracene, 7-Bromomethyl-
DNA Repair
DNA Adducts, 79-6805
L Cells
DNA Repair, 79-6805

Benz(a)anthracene, 3,4-Dihydro-3,4-dihydroxy-7,12-dimethyl-
Sister Chromatid Exchange
Cells, Cultured, 79-6808

Benz(a)anthracene, 7,12-Dimethyl-
Adenocarcinoma
Corn Oil, 79-6817
Dietary Fats, 79-6817
Aryl Hydrocarbon Hydroxylases
Lung Cells, 79-6830
Cell Transformation, Neoplastic
Cells, Cultured, 79-6812
Chromosome Aberrations
Mutagenic Metabolite, 79-6744
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Oxidoreductases, 79-6813
DNA Replication
Liver Regeneration, 79-6864
Fluocinolone Acetonide
DNA, Binding, 79-6803
Gentamicin
Cell Transformation, Neoplastic
79-6823
Gonadotropins
Estrus, Rat, 79-6811
Gynecologic Neoplasms
Hormone Imbalance, 79-6850
HeLa Cells
Ultraviolet Rays, 79-6871
Hepatoma
DNA Adducts, 79-6804
Toxic Metabolites, 79-6804
Indole-3-acetic Acid, 1-(*p*-
Chlorobenzoyl)-5-methoxy-2-
methyl-
DNA, Binding, 79-6803
Lung Neoplasms
Transplacental Carcinogenesis
79-6618
Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6667, 79-6817
Adenofibroma, 79-6667
Ethylene, 1-Bromo-2-(*p*-(ethylphenyl)-
1,2-diphenyl-, 79-6667
Gonadotropins, 79-6811
Hormone Imbalance, 79-6850
Precancerous Conditions, 79-6818
79-6963
Progesterone, 79-6857
Prolactin, 79-6818
R2323, 79-6857
Somatotropin, 79-6811
Thyrotropin, 79-6811
Thyrotropin Releasing Hormone
79-6811
Transplacental Carcinogenesis
79-6618
Virus, Murine Mammary Tumor
79-6969

Melanoma
Neoplasms, Multiple Primary, 79-6850
Mouth Neoplasms
Carcinoma, Epidermoid, 79-6816
Neovascularization, 79-6816
Papilloma, 79-6816
Precancerous Conditions, 79-6816
Ovarian Neoplasms
Castration, Mouse, 79-6810
Transplacental Carcinogenesis
79-6618

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)
Transplantation, Autologous, 79-6810
Oxygen
Photosensitization, 79-6871
Peptides
Cell Transformation, Neoplastic
79-6809
Poly A
Binding, 79-6807
Prolactin
Estrus, Rat, 79-6811
Prostaglandins E
DNA, Binding, 79-6803
Sister Chromatid Exchange
Cells, Cultured, 79-6808
Skin Neoplasms
Aroclor 1254, 79-6813
Azobenzene, 3,3',4,4'-Tetrachloro-
79-6813
Benzo(e)pyrene, 79-6815
Dibenzo-*p*-dioxin, 2,7-Dichloro-
79-6813
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
79-6813
Fluoranthene, 79-6815
Mezerein, 79-6800
Pyrene, 79-6815
12-*O*-Tetradecanoylphorbol-13-acetate
79-6800, 79-6813
4,4'-Stilbenediol, α,α' -Diethyl-
Co-carcinogenic Effect, 79-6850
Stomach Neoplasms
Neoplasms, Multiple Primary, 79-6850
Tracheal Neoplasms
Carcinoma, Epidermoid, 79-6802
79-6814
Carcinoma In Situ, 79-6814
Dose-Response Study, 79-6802
Neoplasm Regression, Spontaneous
79-6814
Precancerous Conditions, 79-6802
79-6814
Transplacental Carcinogenesis
Genetics, Review, 79-6618
Ultraviolet Rays
Cell Survival, 79-6871
DNA Replication, 79-6871
Virus, Murine Mammary Tumor
RNA, Viral, 79-6969

Benz(a)anthracene, 1-Methyl-
Carbon
K-Region Binding, 79-6806
Structure-Activity Relationship
X-Ray Diffraction, 79-6806

Benzaldehyde
Barbituric Acid, 5-Ethyl-5-phenyl-
Metabolism, Rat, 79-6742
Benzylamine, *N*-Methyl-*N*-nitroso-
Microsomes, Liver, 79-6742

Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
Chloramphenicol
Oxidoreductases, 79-6757
Proteins, Binding, 79-6757
Microsomes, Liver
Metabolism, 79-6757
Precancerous Conditions
Liver, Rat, 79-6756
RNA
Liver, Rat, 79-6756
Nucleotide Sequence, 79-6756

Benzenamine, *N*-Hydroxy-*N*-nitroso-, Ammonium Salt
Adrenal Gland Neoplasms
Ganglioneuroma, 79-6754
Angiosarcoma
Dose-Response Study, 79-6754
Ear Neoplasms
Carcinoma, Epidermoid, 79-6754
Eye Neoplasms
Adenoma, 79-6754
Glioma
Dose-Response Study, 79-6754
Hepatoma

Benzenamine, N-Hydroxy-N-nitroso-, Ammonium Salt (cont'd)
 Dose-Response Study, 79-6754
 Stomach Neoplasms
 Carcinoma, Epidermoid, 79-6754

Benzenamine, 2-Methoxy-5-methyl-
 Bladder Neoplasms
 Carcinoma, Epidermoid, 79-6755
 Carcinoma, Transitional Cell, 79-6755
 Cholangioma
 Dose-Response Study, 79-6755
 Ear Neoplasms
 Cholangioma, 79-6755
 Hepatoma
 Dose-Response Study, 79-6755
 Neuroblastoma
 Dose-Response Study, 79-6755

Benzene
 Cholanthrene, 3-Methyl-
 Emission Spectra, 79-6761
 Leukemia
 Occupational Hazard, 79-7176

Benzene, 4-Allyl-1,2-(methylenedioxy)-
 Food Contamination
 Carcinogenic Potential, Review
 79-6614
 Hepatoma
 Neoplasm Metastasis, 79-6748
 Kidney Neoplasms
 Transplacental Carcinogenesis
 79-6748
 Perinatal Carcinogenesis
 Mouse, Review, 79-6609

Benzene, Bromo-
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Epoxide Metabolites, 79-6746
 5,6-Benzoflavone
 Epoxide Metabolites, 79-6746
 Cholanthrene, 3-Methyl-
 Epoxide Metabolites, 79-6746

Benzene, 1,2,4-Trimethoxy-5-(1-propenyl)-
 Food Contamination
 Carcinogenic Potential, Review
 79-6614

Benzenediazosulfonic Acid, p-(Dimethylamino)-, Sodium Salt
 Necrosis
 Kidney Tubules, 79-6656
 Uterine Neoplasms
 Sarcoma, 79-6656

Benzo(a)pyren-3-ol
 Metabolism
 Feces, Rat, 79-6836

Benzo(a)pyrene
 Acetaldehyde
 Co-carcinogenic Effect, 79-6678
 Antibodies
 Hemagglutination Tests, 79-6829
 Mutagenic Activity, 79-6829
 Aryl Hydrocarbon Hydroxylases
 Lung Cells, 79-6830
 Asbestos
 Co-carcinogenic Effect, 79-6831
 Transport, Microsomes, 79-6831
 Carcinoma, Epidermoid
 Cells, Cultured, 79-6833
 Cell Transformation, Neoplastic
 Epidermis, Mouse, 79-6833
 Mathematical Model, 79-7159
 Chromosomal Proteins, Non-Histone
 Binding, 79-6830
 Chromosome Aberrations
 Fedder Cell Induction, 79-6835
 Chromosomes
 Cell Transformation, Neoplastic
 79-6833
 Ploidies, 79-6833
 DNA, Binding
 Lymphocytes, 79-6832
 Food Contamination
 Metabolism, 79-6836

Benzo(a)pyrene (cont'd)
 Quantitation, 79-6840
 Iron Oxide
 Transport, Microsomes, 79-6831
 Keratin
 Cell Transformation, Neoplastic
 79-6833
 Leukemia
 Virus, Friend Murine Leukemia
 79-7070
 Lung Neoplasms
 Virus, Influenza, 79-6633
 Lymphoma
 Lymphocyte Culture Test, Mixed
 79-7070
 Macrophages
 Sister Chromatid Exchange, 79-6834
 Microsomes, Liver
 Carcinogenic Metabolite, 79-6832
 Phenol Metabolites, 79-6837
 Ouabain Resistance
 Carcinogenic Metabolite, 79-6834
 Perinatal Carcinogenesis
 Mouse, Review, 79-6609
 Phenol, (1,1-Dimethylethyl)-4-methoxy-
 DNA, Binding, 79-6832
 Poly A
 Binding, 79-6807
 Quartz
 Transport, Microsomes, 79-6831
 Radiation, Ionizing
 Mathematical Model, 79-7159
 Respiratory Tract Neoplasms
 Adenocarcinoma, 79-6678
 Adenoma, 79-6678
 Sarcoma
 Gamma Globulins, 79-6839
 Serum Albumin, 79-6839
 Tissue Culture
 Carcinogenic Metabolite, 79-6837

Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-
 Metabolism
 Feces, Rat, 79-6836

Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
 Macrophages
 Sister Chromatid Exchange, 79-6834
 Metabolism
 Feces, Rat, 79-6836
 Ouabain Resistance
 Carcinogenic Metabolite, 79-6834

Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
 7,8,9,10-tetrahydro-
 Benzo(e)pyrene
 Carcinogenic Activity, Mouse, 79-6815
 Macrophages
 Sister Chromatid Exchange, 79-6834
 Ouabain Resistance
 Carcinogenic Metabolite, 79-6834

Benzo(a)pyrene-1,6-dione
 Metabolism
 Feces, Rat, 79-6836

Benzo(a)pyrene-3,6-dione
 Metabolism
 Feces, Rat, 79-6836

Benzo(e)pyrene
 Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-
 7,8,9,10-tetrahydro-
 Carcinogenic Activity, Mouse, 79-6815
 Papilloma
 Carcinogenic Activity, Mouse, 79-6815
 Skin Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6815

Benzo(rst)pentaphene
 Excited States
 Fluorescence, 79-6761
 Toluene
 Emission Spectra, 79-6761

5H-Benzocyclohepten-5-one, 2,3,4,6-Tetrahydroxy-
 Ames Test
 Mutagenic Activity, 79-6784
 Colicins
Salmonella typhimurium, 79-6784

1,3-Benzodioxole, 5-(2-(Octylsulfinyl)propyl)-
 Hepatoma
 Carcinogenic Potential, 79-6760

5,6-Benzoflavone
 Aryl Hydrocarbon Hydroxylases
 Lymphocytes, 79-6819
 Benzene, Bromo-
 Epoxide Metabolites, 79-6746
 Hyperplasia
 Acetamide, N-Fluoren-2-yl-, 79-6687

7,8-Benzoflavone
 Aryl Hydrocarbon Hydroxylases
 Lymphocytes, 79-6819
 Hepatoma
 Toxic Metabolites, 79-6804

Benzoic Acid, 2-(Acetyloxy)-
 12- α -Tetradecanoylphorbol-13-acetate
 Prostaglandins E, 79-6795

p-Benzoquinone Dioxide
 Hepatoma
 Dose-Response Study, 79-6763
 Urologic Neoplasms
 Dose-Response Study, 79-6763

Benzyl Chloride
 see Toluene, α -Chloro-

Benzylamine, N-Methyl-N-nitroso-
 Benzaldehyde
 Microsomes, Liver, 79-6742
 Microsomes
 Metabolism, Rat, 79-6742

Beryllium Chloride
 Azaguanine Resistance
 Mutagenic Activity, 79-6652

Bile Acids and Salts
 Pancreatic Neoplasms
 Dipropylamine, 2,2'-Dihydroxy-N-nitroso-, 79-6727

Bile Duct Neoplasms
 Adenocarcinoma
 Cysts, 79-7121
 Carcinoma, Epidermoid
 Cysts, 79-7121

1,1'-Biphenyl, 4,4'-Diisocyanato-3,3'-dimethoxy-
 Ear Neoplasms
 Carcinoma, Epidermoid, 79-6769
 Leukemia
 Carcinogenic Potential, 79-6769
 Lymphoma
 Carcinogenic Potential, 79-6769
 Sebaceous Gland Neoplasms
 Carcinoma, 79-6769
 Skin Neoplasms
 Carcinoma, Epidermoid, 79-6769
 Uterine Neoplasms
 Polyps, 79-6769

4-Biphenylamine
 Bile
 Ames Test, 79-6768
 Mutagenic Metabolite, 79-6768
 Glucuronidase
 Ames Test, 79-6768

4-Biphenylamine, 3,2'-Dimethyl-
 Bile
 Ames Test, 79-6768
 Mutagenic Metabolite, 79-6768

4,4'-Bipyridinium, 1,1'-Dimethyl-, Dichloride
 Ames Test
 Mutagenic Activity, 79-6758
Aspergillus nidulans
 Mutagenic Activity, 79-6758

4,4'-Bipyridinium, 1,1'-Dimethyl-, Dichloride (cont'd)
Lactate Dehydrogenase
Enzymatic Activity, 79-6698

Bladder Neoplasms

Adenocarcinoma
1-Butanol, 4-(Butylnitrosamino)-
79-6733
Alkaline Phosphatase
Precancerous Conditions, Rat, 79-6733
1-Butanol, 4-(Butylnitrosamino)-
4,4'-Stilbenediol, α,α' -Diethyl-
79-6849
Testosterone, 79-6849
Carcinoma, Epidermoid
Benzenamine, 2-Methoxy-5-methyl-
79-6755
1-Butanol, 4-(Butylnitrosamino)-
79-6733
Carcinoma, Transitional Cell
Benzenamine, 2-Methoxy-5-methyl-
79-6755
1-Butanol, 4-(Butylnitrosamino)-
79-6731, 79-6733
Dibutylamine, *N*-Nitroso-, 79-6733
Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-, 79-6733
Genetics, 79-7132
Smoking, 79-7132
Hyperplasia
Precancerous Conditions, Rat, 79-6733
2-Naphthylamine
Cyclophosphamide, 79-6771
Precancerous Conditions, 79-6771
Papilloma
Aflatoxin B1, 79-6790
Precancerous Conditions, Rat, 79-6733

Bleomycin

DNA
Double Strand Breaks, 79-6904

Bloom's Syndrome

see Dwarfism

Bone Marrow

Acetamide, *N*-Fluoren-2-yl-
Chromatids, 79-6686
Cyclophosphamide
Chromatids, 79-6686

Brain Neoplasms

Fibrosarcoma
Radiation, Ionizing, 79-6902
Ganglioneuroma
Urea, Ethyl Nitroso-, 79-6715
Meningioma
Karyotyping, 79-7099
Radiation, Ionizing
Case Report, 79-6902

Breast Neoplasms

Androst-4-ene-3,17-dione
Plasma Levels, 79-7150
Antigens, Neoplasm
Leukocyte Adherence Inhibition Test
79-7093
Neoplasm Metastasis, 79-7093
Blacks
Epidemiology, 79-7157
Carcinoma, Ductal
Virus, Murine Mammary Tumor
79-6968
Cystosarcoma Phyllodes
Case Report, 79-7135
Dehydroepiandrosterone
Plasma Levels, 79-7150
Etiocolanolone
Urine, 79-7150
Genetics
Case Report, 79-7134
Risk Factors, 79-7134
Hair Dyes
Epidemiology, 79-7156
IgM
Immune Response, 79-7149
Plasma Levels, 79-7149
Insulin

Breast Neoplasms (cont'd)

Growth, 79-7200
Peptides
Growth Substances, 79-7200
Prostaglandins F
Growth Substances, 79-7200
Scleroderma
Epidemiology, 79-7158
4,4'-Stilbenediol, α,α' -Diethyl-
Metabolism, 79-6851
Transferrin
Prostaglandins F, 79-7200
Virus, Epstein-Barr
Virus Activation, 79-7019
Virus, Mason-Pfizer Monkey
DNA-RNA Hybridization, 79-6970
Virus, Murine Mammary Tumor
DNA-RNA Hybridization, 79-6970

Broparestrol

see Ethylene, 1-Bromo-2-*p*-(ethyl-phenyl)-1,2-diphenyl-

Burkitt's Lymphoma

Virus, Adeno 4
Antibodies, Viral, 79-7013
Virus, Cytomegalo
Antibodies, Viral, 79-7013
Virus, Epstein-Barr
RNA, Ribosomal, 79-7016
RNA, Viral, 79-7016
Virus, Herpes Simplex 1
Antibodies, Viral, 79-7013
Virus, Measles
Antibodies, Viral, 79-7013

Butane, 1,2:3,4-Diepoxy-

Anemia, Aplastic
Chromosome Aberrations, 79-6670
Ataxia Telangiectasia
Chromosome Aberrations, 79-6670
Chromosome Aberrations
Fibroblasts, 79-6670
Quantitation Method, 79-6744
Xeroderma Pigmentosum
Chromosome Aberrations, 79-6670

1-Butanol, (4-Butylnitrosamino)-

Ames Test
 α -Acetoxy Derivatives, 79-6732
Bladder Neoplasms
Adenocarcinoma, 79-6733
Carcinoma, Epidermoid, 79-6733
Carcinoma, Transitional Cell, 79-6731
79-6733
4,4'-Stilbenediol, α,α' -Diethyl-
79-6849
Testosterone, 79-6849
Carcinoma, Transitional Cell
Hemodynamics, 79-6731
Precancerous Conditions, 79-6731
Transplacental Carcinogenesis
Hamster, 79-6721

2-Butanone

Lymphoma
Air Pollution, 79-7165
Solvents
Epidemiology, 79-7165

Butylamine, *N*-Ethyl-*N*-nitroso-

Food Contamination
Quantitation Method, 79-6729

C.I. Vat Yellow

see Dibenzo(b,def)chrysene-7,12-dione

Cadmium Chloride

Calcium
Chromosome Aberrations, 79-6646
Erythrocytes
Metalloproteins, 79-6645
Lymphocytes
Immune Response, 79-6645
Metalloproteins, 79-6645

Caffeine

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
Cell Transformation, Neoplastic

Caffeine (cont'd)

Cell Transformation, Neoplastic
79-6891
Neoplasms
Co-carcinogenic Effect, 79-7177
Skin Neoplasms
Ultraviolet Rays, 79-6876
Ultraviolet Rays
DNA Repair, 79-6876

Calcium

Acetic Acid, Lead Salt
Chromosome Aberrations, 79-6646
Cadmium Chloride
Chromosome Aberrations, 79-6646
Zinc Chloride
Chromosome Aberrations, 79-6646

Carbadox

Chromatids
Bone Marrow, 79-6735
Chromosome Aberrations
Micronucleus Test, 79-6735

Carbamic Acid, Diethyldithio-, 2-

Chloroallyl Ester
Esophageal Neoplasms
Carcinoma, Epidermoid, 79-6702
Papilloma, 79-6702
Hepatoma
Carcinogenic Potential, 79-6702
Lung Neoplasms
Carcinogenic Potential, 79-6702
Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6702
Stomach Neoplasms
Carcinoma, Epidermoid, 79-6702
Thyroid Neoplasms
Adenocarcinoma, 79-6702

Carbamic Acid, Ethyl Ester

Lactate Dehydrogenase
Lung, Mouse, 79-6698
Lung Neoplasms
Adenoma, 79-6699
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6699
Virus, Influenza, 79-6633

Carbamic Acid, Ethylnitroso-, Ethyl Ester

Digestive System Neoplasms
Histological Study, Rat, 79-6701
Skin Neoplasms
Histological Study, Rat, 79-6701

Carbamic Acid, Methyl-, α -

Isopropoxyphenyl Ester
Cell Transformation, Neoplastic
N-Nitroso Derivatives, 79-6812

Carbamic Acid, Methyl-, 1-Naphthyl Ester

Cell Transformation, Neoplastic
Embryo, Hamster, 79-6812

Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester

Ames Test
Mutagenic Activity, 79-6700
Cell Transformation, Neoplastic
Cells, Cultured, 79-6812
Lymphocytes
Azaguanine Resistance, 79-6700

Carbamic Acid, Methyl-, Trimethylphenyl Ester

Cell Transformation, Neoplastic
N-Nitroso Derivatives, 79-6812

Carbamic Acid, Nitrosopentyl-, Ethyl Ester

Mouth Neoplasms
Histological Study, Rat, 79-6701
Pharyngeal Neoplasms
Structure-Activity Relationship
79-6701

Carbofuran, *N*-Nitroso-

Cell Transformation, Neoplastic
Embryo, Hamster, 79-6812

Carbon

Benz(a)anthracene, 1-Methyl-
K-Region Binding, 79-6806

Carbon Tetrabromide
Lung Neoplasms
Carcinogenic Activity, Mouse, 79-6666
Stomach Neoplasms
Carcinogenic Activity, Mouse, 79-6666

Carcinogen, Chemical

Adenosine
Benzoylation, 79-6740
Cell Transformation, Neoplastic
Fibroblasts, Review, 79-6630
Parametric Excitation, Review
79-6606
DNA
Spectrum Analysis, Raman, Review
79-6606
DNA Repair
Cell Transformation, Neoplastic, Review, 79-6626
Guanosine
Benzoylation, 79-6740
Hodgkin's Disease
Occupational Hazard, 79-7154
Mathematical Model
Dose-Response Study, Review
79-6603
Mutation
DNA Repair, Review, 79-6605
Transplacental Carcinogenesis
Mouse, Rat, Review, 79-6619
Ultraviolet Rays
Co-carcinogenic Effect, Review
79-6624

Carcinogen, Environmental

Cell Transformation, Neoplastic
Mutagenic Activity, Review, 79-6604
Chromosome Aberrations
Genes, Regulatory, Review, 79-6604
Ultraviolet Rays
Photochemistry, Review, 79-6624
Urologic Neoplasms
Nephritis, Interstitial, 79-6615

Carcinoma

Adrenal Gland Neoplasms
Phosphorothioic Acid, *O,O*-Diethyl *O*-(*p*-Nitrophenyl) Ester, 79-6765
Cervix Neoplasms
Virus, Herpes Simplex 2, 79-7008
Gallbladder Neoplasms
Aflatoxin B1, 79-6790
Gastrointestinal Neoplasms
Peutz-Jeghers Syndrome, 79-7130
Gynecologic Neoplasms
Dieneestrol, 79-7174
Phenol, 4,4'-(1,2-Diethylene)di-, *meso*-
79-7174
4,4'-Stilbenediol, α,α' -Diethyl-
79-7174
Kidney Neoplasms
Dimethylamine, *N*-Nitroso-, 79-6863
Virus, DNA Tumor, 79-7051
Lung Neoplasms
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6753
Mammary Neoplasms, Experimental
Mucopolysaccharides, 79-7199
Pancreatic Neoplasms
Aflatoxin B1, 79-6790
Respiratory Tract Neoplasms
Ethanol, *N*-Nitrosoiminodi-, 79-6611
Nicotine, 1'-Demethyl-1'-nitroso-
79-6611
Sebaceous Gland Neoplasms
1,1'-Biphenyl, 4,4'-Diisocyanato-
3,3'-dimethoxy-, 79-6769
Stomach Neoplasms
Gastrectomy, 79-7129
Thyroid Neoplasms
Phosphamidon, 79-6655
Radiation, Ionizing, 79-7166
Tracheal Neoplasms
Cholanthrene, 3-Methyl-, 79-6824
79-6825
Fibrosarcoma, 79-6824, 79-6825
Precancerous Conditions, 79-6710
Urea, Methyl Nitroso-, 79-6710
Uterine Neoplasms

Carcinoma (cont'd)

Histological Study, 79-7171
Virus, Herpes Simplex 2
Antigens, Viral, 79-7008
Peptides, 79-7008

Carcinoma, Basal Cell

Hemangioma
Radiotherapy, 79-6905
Radiation, Ionizing
Case Report, 79-6905
Skin Neoplasms
Arsenic, 79-6644
Carcinoma, Epidermoid, 79-7168
Uracil, 5-Fluoro-
Neoplasm Recurrence, Local, 79-6738

Carcinoma, Bronchiolar

Age Factors
Epidemiology, 79-7138

Carcinoma, Bronchogenic

Age Factors
Epidemiology, 79-7138
Precancerous Conditions
Histological Study, Hamster, Review
79-6638
Respiratory Tract Neoplasms
Morpholine, 2,6-Dimethyl-*N*-nitroso-
79-6612
Morpholine, *N*-Nitroso-, 79-6612
Piperidine, 1-Nitroso-, 79-6612

Carcinoma, Clear Cell

see Adenocarcinoma

Carcinoma, Ductal

Breast Neoplasms
Virus, Murine Mammary Tumor
79-6968
Mammary Neoplasms, Experimental
Chondroitin, 79-7199
Hyaluronic Acid, 79-7199
Pancreatic Neoplasms
Ultrastructural Study, 79-7125
Virus, Murine Mammary Tumor
Virus Replication, 79-6968

Carcinoma, Ehrlich Tumor

Cyclophosphamide, 4-Hydroperoxy-
Photon Absorption, Review, 79-6601
Radiation, Ionizing
Growth, 79-6906
Leukocytosis, Tissue, 79-6906

Carcinoma, Epidermoid

Benzo(a)pyrene
Cells, Cultured, 79-6833
Bile Duct Neoplasms
Cysts, 79-7121
Bladder Neoplasms
Benzenamine, 2-Methoxy-5-methyl-
79-6755
1-Butanol, 4-(Butylnitrosamino)-
79-6733
Cervix Neoplasms
Condylomata Acuminata, 79-7062
Epidemiology, 79-7136
Condylomata Acuminata
Case Report, 79-7062
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Dose-Response Study, Rat, 79-6773
Ear Neoplasms
Benzenamine, *N*-Hydroxy-*N*-nitroso-,
Ammonium Salt, 79-6754
1,1'-Biphenyl, 4,4'-Diisocyanato-
3,3'-dimethoxy-, 79-6769
p-Toluidine, *N*-Isopropyl- α -(2-
methylhydrazino)-, 79-6750
Epidermodysplasia Verruciformis
Case Report, 79-7030
Erythema
Case Report, 79-6911
Esophageal Neoplasms
Carbamic Acid, Diethylidithio-, 2-
Chloroallyl Ester, 79-6702
Hodgkin's Disease
Immunologic Deficiency Syndromes
79-7088

Carcinoma, Epidermoid (cont'd)

Keratin
Heat, 79-6911
Laryngeal Neoplasms
Radiation, Ionizing, 79-7140
Lip Neoplasms
Lupus Erythematosus, Discoid
79-7103
Lung Neoplasms
Antigens, Neoplasm, 79-7091
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
79-6773
Epidemiology, 79-7138
Polonium, 79-6922
Radioisotopes, 79-6896
Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6816
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
79-6773
Epidemiology, Review, 79-6640
Ethyl Alcohol, 79-6640
Smoking, 79-6640
Virus, Herpes Simplex 1, 79-6641
Neoplasms, Multiple Primary
Hodgkin's Disease, 79-7088
Pharyngeal Neoplasms
Epidemiology, Review, 79-6640
Ethyl Alcohol, 79-6640
Radiation, Ionizing, 79-6912, 79-7140
Skin Neoplasms
Arsenic, 79-6644
1,1'-Biphenyl, 4,4'-Diisocyanato-
3,3'-dimethoxy-, 79-6769
Carcinoma, Basal Cell, 79-7168
Saudi Arabia, 79-7146
Ultraviolet Rays, 79-6885, 79-6889
79-7168
Smoking
Age Factors, 79-7138
Stomach Neoplasms
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-
furyl)-, 79-6690
Benzenamine, *N*-Hydroxy-*N*-nitroso-,
Ammonium Salt, 79-6754
Carbamic Acid, Diethylidithio-, 2-
Chloroallyl Ester, 79-6702
Propene, 3-Chloro-, 79-6669
Tracheal Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6802, 79-6814
Diethylamine, *N*-Nitroso-, 79-6725
Precancerous Conditions, 79-6710
Urea, Methyl Nitroso-, 79-6708
Ultraviolet Rays
Dose-Response Study, 79-6882
Uracil, 5-Fluoro-
Case Report, 79-6738
Uterine Neoplasms
Histological Study, 79-7171

Carcinoma In Situ
Skin Neoplasms
Ultraviolet Rays, 79-6889
Tracheal Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6814

Carcinoma, Mucinous
Intestinal Neoplasms
Radiation, Ionizing, 79-6917
Stomach Neoplasms
NADH, NADPH Oxidoreductases
79-7128

Carcinoma, Oat Cell
Lung Neoplasms
Epidemiology, 79-7138
Ultrastructural Study, 79-7119

Carcinoma, Papillary
Carcinoma, Transitional Cell
Benzenamine, 2-Methoxy-5-methyl-
79-6755
Thyroid Neoplasms
1,5-Naphthalenediamine, 79-6772
Radiation, Ionizing, 79-6901

Carcinoma, Transitional Cell

Benzenamine, 2-Methoxy-5-methyl-
Dose-Response Study, 79-6755

Bladder Neoplasms

Benzenamine, 2-Methoxy-5-methyl-
79-6755

1-Butanol, 4-(Butylnitrosamino)-
79-6731, 79-6733

Dibutylamine, *N*-Nitroso-, 79-6733

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-
thiazolyl)-, 79-6733

Genetics, 79-7132

Smoking, 79-7132

1-Butanol, 4-(Butylnitrosamino)-
Hemodynamics, 79-6731

Precancerous Conditions, 79-6731

Carcinoma, Papillary

Benzenamine, 2-Methoxy-5-methyl-
79-6755

Genetics

Case Report, 79-7132

2-Naphthylamine

Cyclophosphamide, 79-6771

Urogenital Neoplasms

o-Toluidine, Hydrochloride, 79-6752

Carcinoma 256, Walker**Dextrans**

Neoplasm Metastasis, 79-6657

Turpentine

Wounds and Injuries, 79-6657

Wounds and Injuries

Neoplasm Metastasis, 79-6657

Cecal Neoplasms**Intestinal Neoplasms**

Radiotherapy, 79-6917

Cell Adhesion**Leukemia, Myelocytic**

Teleocidin B, Dihydro, 79-6844

Mesenchymoma

Fibroblasts, 79-7118

Cell Differentiation**Erythroleukemia**

Teleocidin B, Dihydro, 79-6844

Leukemia, Myeloblastic

Granulocytes, 79-7193

Leukemia, Myelocytic

Granulocytes, 79-7073

Muramidase, 79-6796

Phorbol Esters, 79-6796

Rosette Formation, 79-6796

12-*O*-Tetradecanoylphorbol-13-acetate

79-6794, 79-6796

Sarcoma, Osteogenic

Ultrastructural Study, 79-7115

Stomach Neoplasms

Prognosis, 79-7128

12-*O*-Tetradecanoylphorbol-13-acetate

Lipopolysaccharides, 79-6796

Tracheal Neoplasms

Endoplasmic Reticulum, 79-6725

Urea, Ethyl Nitroso-

Carcinogenic Activity, Opossum

79-6715

Virus, AKR Murine Leukemia

T-Lymphocytes, 79-7069

Virus, Avian Leukemia

Bone Marrow, 79-6929

Virus, Friend Murine Leukemia

Granulocytes, 79-7073

Virus, Moloney Murine Leukemia

Virus Activation, 79-6986

Virus, Rous Sarcoma

Myosin, 79-6945

Cell Division**Hepatoma**

Dimethylamine, *N*-Nitroso-, 79-6864

12-*O*-Tetradecanoylphorbol-13-acetate

Clostridiopeptidase A, 79-6795

Cell Fusion**Virus, Rous Sarcoma**

Replication-Defective Mutants

79-6949

Virus, SV40

Cell Fusion (cont'd)

Virus Rescue, 79-7035

Cell Membrane**Cell Transformation, Neoplastic**

Abnormal Film Matrix, Review

79-6632

Lymphoma

Virus, Newcastle Disease, 79-7061

Virus, Sendai, 79-7061

Virus, Adeno 12

Antigens, 79-7048

Antigens, Viral, 79-7049

Virus, Avian Sarcoma

Viral Proteins, 79-6932

Virus, Polyoma

Antigens, Neoplasm, 79-7029

Virus, Rauscher Murine Leukemia

Glycoproteins, 79-6992

Virus, Rous Sarcoma

Antigens, Neoplasm, 79-6950

Cell Survival**HeLa Cells**

Ultraviolet Rays, 79-6871

Ultraviolet Rays

Benz(a)anthracene, 7,12-Dimethyl-

79-6871

Cell Transformation, Neoplastic

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-

yl-

Caffeine, 79-6891

Aldicarb

N-Nitroso Derivatives, 79-6812

Benz(a)anthracene, 7,12-Dimethyl-

Cells, Cultured, 79-6812

Gentamicin, 79-6823

Peptides, 79-6809

Benzo(a)pyrene

Chromosomes, 79-6833

Epidermis, Mouse, 79-6833

Keratin, 79-6833

Mathematical Model, 79-7159

Carbamic Acid, Methyl-, *o*-

Isopropoxyphenyl Ester

N-Nitroso Derivatives, 79-6812

Carbamic Acid, Methyl-, 1-Naphthyl Es-

ter

Embryo, Hamster, 79-6812

Carbamic Acid, *N*-Methyl-*N*-nitroso-,

Ethyl Ester

Cells, Cultured, 79-6812

Carbamic Acid, Methyl-, Trimethylphe-

nyl Ester

N-Nitroso Derivatives, 79-6812

Carbofuran, *N*-Nitroso-

Embryo, Hamster, 79-6812

Carcinogen, Chemical

Fibroblasts, Review, 79-6630

Parametric Excitation, Review

79-6606

Carcinogen, Environmental

Mutagenic Activity, Review, 79-6604

Cell Membrane

Abnormal Film Matrix, Review

79-6632

Cells, Cultured

Phenotype, Review, 79-6630

Cholanthrene, 3-Methyl-

Gentamicin, 79-6823

Penicillin G, Sodium Salt, 79-6823

Diethylamine, *N*-Nitroso-

Cells, Cultured, 79-6812

Dipyrido(1,2-*a*:3',2'-*d*)imidazole, 2-

Amino-6-methyl-

Dose-Response Study, 79-6737

Electromagnetics

Photon Absorption, Review, 79-6601

Foreign Bodies

Abnormal Film Matrix, Review

79-6632

Glutamic Acid

Pyrolysis Product, 79-6737

Insulin

Cell Cycle Kinetics, 79-7187

Interferon

Antiviral Effects, 79-6983

Cell Transformation, Neoplastic (cont'd)

Fibroblasts, 79-6983

Light

Oxygen, 79-6894

Methanesulfonic Acid, Ethyl Ester

Peptides, 79-7187

Methomyl, *N*-Nitroso-

Embryo, Hamster, 79-6812

Mutation

DNA Repair, Review, 79-6605

Oncogenic Viruses

Cells, Cultured, Review, 79-6617

Peptides

Epidermal Growth Factors, 79-6809

Growth Substances, 79-7187

Plasmacytoma

Virus-Like Particles, 79-7055

Polycyclic Hydrocarbons

Cells, Cultured, Review, 79-6617

Radiation, Ionizing

Dose-Response Study, 79-6807

Fibroblasts, Review, 79-6630

Gentamicin, 79-6823

Mathematical Model, 79-6897

Transferrin

Cell Cycle Kinetics, 79-7187

Ultraviolet Rays

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-

2-yl-, 79-6891

Cholanthrene, 3-Methyl-, 79-6883

DNA Photolyase, 79-6874

Dose-Response Study, 79-6883

12-*O*-Tetradecanoylphorbol-13-acetate

79-6883

Virus, Adeno 5

12-*O*-Tetradecanoylphorbol-13-acetate

79-6801

Virus, Adeno 12

Antigens, Viral, 79-7049

DNA, Viral, 79-7046, 79-7048

Histocompatibility Antigens, 79-7048

Virus, AKR Murine Leukemia

Thymus Extracts, 79-7069

Virus, Avian Leukemia

Hematopoietic Stem Cells, 79-6928

79-6929

Virus, Avian Myelocytomatosis

Viral Proteins, 79-6931

Virus, Avian Sarcoma

Phosphoproteins, 79-6936

Tosyllysine Chloromethyl Ketone

79-6933

Viral Proteins, 79-6932

Virus, CELO

Virus-Like Particles, 79-7059

Virus, DNA Tumor

Cells, Cultured, 79-7051

Virus, Epstein-Barr

Antibody Formation, 79-7015

Virus, Herpes Simplex

4,4'-Stilbenediol, α,α' -Diethyl-

79-7011

Virus, Kirsten Murine Leukemia

Interferon, 79-6983

Virus, Kirsten Murine Sarcoma

Cholesterol, 79-6841

Fatty Acids, 79-6841

Virus, Murine Sarcoma

Interferon, 79-6983

Virus, Polyoma

Deletion Mutants, 79-7021, 79-7026

Membrane Proteins, 79-7029

Virus, Rous Sarcoma

Antigens, Neoplasm, 79-6951

Dibutyryl Cyclic AMP, 79-6950

Protein Arginine Methyltransferase

79-6939

Temperature Sensitive Mutants

79-6945

12-*O*-Tetradecanoylphorbol-13-acetate

79-6950

Virus Replication, 79-6940

Cells, Cultured**Carcinoma, Epidermoid**

Benzo(a)pyrene, 79-6833

Light

Cells, Cultured (cont'd)
 Chromosome Aberrations, 79-6894
 Plant Tumors
 Radiation, Ionizing, 79-6898

Cervix Neoplasms
 Adenocarcinoma
 Epidemiology, 79-7136
 Carcinoma
 Virus, Herpes Simplex 2, 79-7008
 Carcinoma, Epidermoid
 Condylomata Acuminata, 79-7062
 Epidemiology, 79-7136
 Precancerous Conditions
 Epidemiology, Colombia, 79-7185

Chloramphenicol
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 Oxidoreductases, 79-6757
 Proteins, Binding, 79-6757
 Ultraviolet Rays
 DNA Repair, 79-6622

5 β -Cholan-24-oic Acid, 3 α ,12 α -Dihydroxy-
 Colonic Neoplasms
 Cholecystectomy, 79-6631

Cholangioma
 Benzenamine, 2-Methoxy-5-methyl-
 Dose-Response Study, 79-6755
 Ear Neoplasms
 Benzenamine, 2-Methoxy-5-methyl-
 79-6755

Cholanthren-2-ol, 3-Methyl-
 Microsomes, Liver
 DNA Adducts, 79-6828

Cholanthrene, 7,8-Dihydro-7,8-dihydroxy-3-methyl-
 Sister Chromatid Exchange
 Cells, Cultured, 79-6808

Cholanthrene, 9,10-Dihydro-9,10-dihydroxy-3-methyl-
 Microsomes, Liver
 DNA Adducts, 79-6828
 Sister Chromatid Exchange
 Cells, Cultured, 79-6808

Cholanthrene, 11,12-Dihydro-11,12-dihydroxy-3-methyl-
 Microsomes, Liver
 DNA Adducts, 79-6828

Cholanthrene, 3,11-Dimethyl-Papilloma
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6827

Cholanthrene, 3-Methyl-
 Aryl Hydrocarbon Hydroxylases
 Lung Cells, 79-6830
 Lymphocytes, 79-6819
 Benzene
 Emission Spectra, 79-6761
 Benzene, Bromo-
 Epoxide Metabolites, 79-6746
 Chromosome Aberrations
 Mutagenic Metabolite, 79-6744
 Concanavalin A
 Immune Response, 79-7080
 Cycloheximide
 Cytochrome P-448, 79-6821
 Microsomes, Liver, 79-6821
 Mixed Function Oxidases, 79-6821
 DNA Adducts
 Lung, Liver, 79-6828
 Excited States
 Fluorescence, 79-6761
 Fibrosarcoma
Corynebacterium parvum, 79-6907
 Radiation, Ionizing, 79-6907
 Gastrointestinal Neoplasms
 Animal Model, Hamster, 79-6822
 Gentamicin
 Cell Transformation, Neoplastic
 79-6823
 Hyperplasia

Cholanthrene, 3-Methyl- (cont'd)
 Acetamide, *N*-Fluoren-2-yl-, 79-6687
 Mammary Neoplasms, Experimental
 Animal Model, Hamster, 79-6822
 Cystadenoma, Papillary, 79-6826
 Neoplasm Metastasis, 79-6826
 Microsomes, Liver
 DNA Adducts, 79-6828
 Neoplasms, Experimental
 Immunologic Techniques, 79-7066
 Papilloma
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6827
 Penicillin G, Sodium Salt
 Cell Transformation, Neoplastic
 79-6823
 Sarcoma
 Lymphocyte Culture Test, Mixed
 79-7070
 T-Lymphocytes, 79-7082
 Sister Chromatid Exchange
 Cells, Cultured, 79-6808
 Tracheal Neoplasms
 Asbestos, 79-6824, 79-6825
 Carcinoma, 79-6824, 79-6825
 Fibrosarcoma, 79-6824, 79-6825
 Iron Oxide, 79-6824, 79-6825
 Ultraviolet Rays
 Cell Transformation, Neoplastic
 79-6883

Cholecalciferol
 Aryl Hydrocarbon Hydroxylases
 Lymphocytes, 79-6819

Cholesterol
 Adenocarcinoma
 Hydroxymethylglutaryl CoA Reductases, 79-7197
 Pentanoic Acid, 3,5-Dihydroxy-3-methyl-, 79-7197
 Squalene, 79-7197
 Kidney Neoplasms
 Adenocarcinoma, 79-7197
 Ultraviolet Rays
 Carcinogenic Activity, 79-6888
 Virus, Kirsten Murine Sarcoma
 Cell Transformation, Neoplastic
 79-6841

Choline
 Liver Neoplasms
 Serine, Diazoacetate (Ester), 79-6683
 Serine, Diazoacetate (Ester)
 Glutamyltranspeptidase, 79-6683

Chondroitin
 Mammary Neoplasms, Experimental
 Carcinoma, Ductal, 79-7199

Choriocarcinoma
 Epidemiology
 Greenland, 79-7147
 Gonadotropins, Chorionic
 Isolation and Characterization
 79-7189

Chromatids
 Acetamide, *N*-Fluoren-2-yl-
 Bone Marrow, 79-6686
 Liver Regeneration, 79-6686
 Carbadox
 Bone Marrow, 79-6735
 Cyclophosphamide
 Bone Marrow, 79-6686
 Liver Regeneration, 79-6686
 Estradiol, 17-Ethynyl-
 Lymphocytes, 79-6856
 Mutagenic Activity, 79-6856
 Ethylene, Chloro-
 Mutagenic Activity, 79-6662
 Norgestrel
 Lymphocytes, 79-6856
 Mutagenic Activity, 79-6856
 Ultrasonics
 Lymphocytes, 79-6925
 Metaphase, 79-6925

Chromosome Aberrations
 Acetamide, *N*-Fluoren-2-yl-
 Mutagenic Metabolite, 79-6744
 Acetic Acid, Lead Salt
 Calcium, 79-6646
 Amprolium
 Micronucleus Test, 79-6735
 Anemia, Aplastic
 Butane, 1,2:3,4-Diepoxy-, 79-6670
 Ataxia Telangiectasia
 Butane, 1,2:3,4-Diepoxy-, 79-6670
 Azathioprine
 Drug Therapy, 79-6781
 Lymphocytes, 79-6781
 Benz(a)anthracene, 7,12-Dimethyl-
 Mutagenic Metabolite, 79-6744
 Benzo(a)pyrene
 Fedder Cell Induction, 79-6835
 Butane, 1,2:3,4-Diepoxy-
 Fibroblasts, 79-6670
 Quantitation Method, 79-6744
 Cadmium Chloride
 Calcium, 79-6646
 Carbadox
 Micronucleus Test, 79-6735
 Carcinogen, Environmental
 Genes, Regulatory, Review, 79-6604
 Cholanthrene, 3-Methyl-
 Mutagenic Metabolite, 79-6744
 Coloboma
 Chromosomes, Human, 13-15, 79-7102
 Cyclophosphamide
 Mutagenic Metabolite, 79-6744
 Ethylene, Chloro-
 Lymphocytes, 79-6662
 Occupational Hazard, 79-6662
 Griseofulvin
 Bone Marrow, 79-6785
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Quantitation Method, 79-6744
 3-Heptanone, 6-(Dimethylamino)-4,4-diphenyl-, Hydrochloride
 Spermatozoa, 79-6671
 Imidazole, 1,2-Dimethyl-5-nitro-
 Micronucleus Test, 79-6735
 1-*H*-Imidazole-2-methanol, 1-Methyl-5-nitro-, Carbamate (Ester)
 Micronucleus Test, 79-6735
 Kidney Neoplasms
 Chromosomes, Human, 4-5, 79-7127
 Chromosomes, Human, 6-12, 79-7127
 Lens Diseases
 Coloboma, 79-7102
 Leukemia, Myeloblastic
 Chromosomes, Human, 4-5, 79-7106
 Light
 Cells, Cultured, 79-6894
 Meningioma
 Mitosis, 79-7099
 Methotrexate
 Bone Marrow, 79-6783
 Micronucleus Test, 79-6783
 Nephroblastoma
 Aniridia, 79-7126
 Chromosomes, Human, 6-12, 79-7126
 Propane, 1-Chloro-2,3-epoxy-
 Quantitation Method, 79-6744
 Propane, 1,2-Epoxy-
 Quantitation Method, 79-6744
 Quinoline, 4-Nitro-, 1-Oxide-
 Quantitation Method, 79-6744
 Radiation, Ionizing
 Case Report, 79-6910
 DNA Repair, 79-6629
 Occupational Hazard, 79-6910
 Retinoblastoma
 Chromosomes, Human, 13-15, 79-7102
 Lymphocytes, 79-7101
 Xeroderma Pigmentosum
 Butane, 1,2:3,4-Diepoxy-, 79-6670
 Radiation, Ionizing, 79-6629
 Zinc Chloride
 Calcium, 79-6646

Chromosome Abnormalities
 Leukemia, Lymphoblastic
 Telangiectasis, 79-7109

Chromosomes

- Benzo(a)pyrene
 - Cell Transformation, Neoplastic 79-6833
- Ploidies, 79-6833
- Hybrid Cells
 - Gene Transfer, 79-7186
- Hypoxanthine Phosphoribosyltransferase
 - Gene Transfer, 79-7186
- Teratoid Tumor
 - Histocompatibility Antigens, 79-7079
- Virus, AKR Murine Leukemia
 - Vertical Transmission, 79-6989
- Virus, Moloney Murine Leukemia
 - Vertical Transmission, 79-6989

Chromosomes, Human, 4-5

- Kidney Neoplasms
 - Chromosome Aberrations, 79-7127
- Leukemia, Myeloblastic
 - Chromosome Aberrations, 79-7106

Chromosomes, Human, 6-12

- Kidney Neoplasms
 - Chromosome Aberrations, 79-7127
- Nephroblastoma
 - Chromosome Aberrations, 79-7126
 - Glutathione Reductase, 79-7126
 - Lactate Dehydrogenase, 79-7126
- Virus, Baboon C-Type RNA Tumor
 - Virus Replication, 79-7002

Chromosomes, Human, 13-15

- Coloboma
 - Chromosome Aberrations, 79-7102
- Retinoblastoma
 - Chromosome Aberrations, 79-7102

Chromosomes, Human, 19-20

- Virus, Baboon C-Type RNA Tumor
 - Virus Replication, 79-7002

Chromosomes, Human, 21-22

- Leukemia, Myelocytic
 - Blast Crisis, 79-7107
- Meningioma
 - Monosomy, 79-7099

Chrysene

- Liver Neoplasms
 - Carcinogenic Activity, Mouse, 79-6861

Chrysene, 1,2-Dihydro-1,2-dihydroxy-

- Lung Neoplasms
 - Neoplasms, Multiple Primary, 79-6861

Chrysene, 3,4-Dihydro-3,4-dihydroxy

- Lung Neoplasms
 - Neoplasms, Multiple Primary, 79-6861

Chrysene, 1,2-Dihydroxy-3,4-oxy-1,2,3,4-tetrahydro-

- Lung Neoplasms
 - Neoplasms, Multiple Primary, 79-6861

Citric Acid, Iron Salt

- Plutonium
 - Adsorption, Excretion, 79-6924

Citrulline

- Nephroblastoma
 - Nitrous Acid, Sodium Salt, 79-6607
- Nitrous Acid, Sodium Salt
 - Transplacental Carcinogenesis, Review 79-6607

Clostridiopeptidase A

- 12-O-Tetradecanoylphorbol-13-acetate
 - Cell Division, 79-6795
- Fibroblasts, 79-6795

Cobalt Chloride

- Azaguanine Resistance
 - Mutagenic Activity, 79-6652

Coloboma

- Chromosome Aberrations
 - Chromosomes, Human, 13-15, 79-7102
- Fibroblasts
 - Radiosensitivity, 79-7102
- Lens Diseases
 - Chromosome Aberrations, 79-7102

Colobus polykomos

- Virus, C-Type RNA Tumor
 - Antigenic Determinants, 79-7057
 - Isolation and Characterization 79-7057

Colonic Neoplasms

- Adenocarcinoma
 - Radiation, Ionizing, 79-6918
 - Rectocolitis, 79-6919
 - Surgery, Operative, 79-6919
 - Urinary Diversion, 79-6920
- Virus, Cytomegalo, 79-7012
- Antigens, Neoplasm
 - Leukocyte Adherence Inhibition Test 79-7093
 - Neoplasm Metastasis, 79-7093
- 5 β -Cholan-24-oic Acid, 3 α ,12 α -Dihydroxy-
 - Cholecystectomy, 79-6631
- Cholecystectomy
 - Review, 79-6631
- Hydrazine, 1,2-Dimethyl-
 - Cholecystectomy, 79-6631
- Nephroblastoma
 - Radiotherapy, 79-6918
- Occupational Hazard
 - Epidemiology, 79-7176
- Urinary Diversion
 - Case Report, 79-6920

Concanavalin A

- Cholanthrene, 3-Methyl-
 - Immune Response, 79-7080
- Neoplasms, Experimental
 - Growth, 79-7080
- Plasmacytoma
 - Immune Response, 79-7080
- Virus, Moloney Murine Sarcoma
 - Immune Response, 79-7080

Condylomata Acuminata

- Carcinoma, Epidermoid
 - Case Report, 79-7062
- Cervix Neoplasms
 - Carcinoma, Epidermoid, 79-7062

Contact Inhibition

- Granulocytes
 - Macrophages, 79-7193
- Ultraviolet Rays
 - DNA Replication, 79-6870

Contraceptives, Oral

- Liver Neoplasms
 - Adenoma, 79-6855
 - Histological Study, 79-6855
 - Hyperplasia, 79-6855
- Transplacental Carcinogenesis
 - Bioassays, Review, 79-6620

Cordycepin

- see* Adenosine, 3'-Deoxy-

Corn Oil

- Adenocarcinoma
 - Benz(a)anthracene, 7,12-Dimethyl- 79-6817

Cortisol Acetate

- Fibrosarcoma
 - Neoplasm Metastasis, 79-7083

Corynebacterium parvum

- Fibrosarcoma
 - Cholanthrene, 3-Methyl-, 79-6907

p-Cresidine

- see* Benzenamine, 2-Methoxy-5-methyl-

p-Cresol, 2,6-Di-tert-butyl-

- Intestinal Neoplasms
 - Hydrazine, 1,2-Dimethyl-, 79-6674
- Lactate Dehydrogenase
 - Enzymatic Activity, 79-6698
- Liver Neoplasms
 - Carcinogenic Potential, 79-6753
- Lung Neoplasms
 - Adenoma, 79-6753
 - Carbamic Acid, Ethyl Ester, 79-6699

p-Cresol, 2,6-Di-tert-butyl- (cont'd)

- Carcinogenic Potential, 79-6753
- Carcinoma, 79-6753
- Hydrazine, 1,2-Dimethyl-, 79-6674

Cupferron

- see* Benzenamine, N-Hydroxy-N-nitroso-, Ammonium Salt

Cyanamide, Calcium Salt

- Adrenal Gland Neoplasms
 - Dose-Response Study, 79-6647
- Angiosarcoma
 - Dose-Response Study, 79-6647
- Leukemia
 - Carcinogenic Potential, 79-6647
- Lymphoma
 - Carcinogenic Potential, 79-6647
- Thyroid Neoplasms
 - Precancerous Conditions, 79-6647

Cycloheximide

- Cholanthrene, 3-Methyl-
 - Cytochrome P-448, 79-6821
 - Microsomes, Liver, 79-6821
 - Mixed Function Oxidases, 79-6821
- MSH
 - Tyrosinase, 79-7194
- Virus, Moloney Murine Leukemia
 - Virus Replication, 79-6985

Cyclophosphamide

- Adenocarcinoma
 - Guanidine, 1-Methyl-3-nitro-1-nitroso- 79-6866
- Bladder Neoplasms
 - 2-Naphthylamine, 79-6771
- Carcinoma, Transitional Cell
 - 2-Naphthylamine, 79-6771
- Chromatids
 - Bone Marrow, 79-6686
 - Liver Regeneration, 79-6686
- Chromosome Aberrations
 - Mutagenic Metabolite, 79-6744
- Hepatoma
 - 2-Naphthylamine, 79-6771

Cyclophosphamide, 4-Hydroperoxy-

- Carcinoma, Ehrlich Tumor
 - Photon Absorption, Review, 79-6601

Cystadenoma

- Mammary Neoplasms, Experimental
 - Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)- 79-6713

Cystadenoma, Papillary

- Mammary Neoplasms, Experimental
 - Cholanthrene, 3-Methyl-, 79-6826
- Thyroid Neoplasms
 - 1,5-Naphthalenediamine, 79-6772

Cysteine

- Urea, 1,1'-Ethylenebis(1-nitroso)-
 - Polylysine, Binding, 79-6707
- Urea, Methyl Nitroso-
 - Polylysine, Binding, 79-6707

Cystosarcoma Phylloides

- Breast Neoplasms
 - Case Report, 79-7135

Cysts

- Bile Duct Neoplasms
 - Adenocarcinoma, 79-7121
 - Carcinoma, Epidermoid, 79-7121
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Testis, Mouse, 79-6846

Cytochrome P-448

- Cholanthrene, 3-Methyl-
 - Cycloheximide, 79-6821

Cytochrome P-450

- Acetanilide, 4'-(-p-Fluorophenyl)-
 - Liver, Rat, 79-6689
- Drugs
 - Hepatotoxicity, Review, 79-6616

- Dapsone**
see Aniline, 4,4'-Sulfonyldi-
- Dehydroepiandrosterone**
Breast Neoplasms
Plasma Levels, 79-7150
- Deoxyribonuclease**
Virus, Epstein-Barr
DNA Replication, 79-7014
B-Lymphocytes, 79-7014
- Deoxyribonucleosides**
Urea, Methyl Nitroso-
DNA Replication, 79-6705
- Dexamethasone**
Growth Substances
Granulocytes, 79-6794
- Dextrans**
Carcinoma 256, Walker
Neoplasm Metastasis, 79-6657
- Diallylamine, N-Nitroso-**
Respiratory Tract Neoplasms
Hamster, Review, 79-6610
- Diazinon**
Dose-Response Study
Carcinogenic Potential, 79-6764
- Dibenz(a,c)anthracene**
Poly A
Binding, 79-6807
- Dibenz(a,h)anthracene**
Aryl Hydrocarbon Hydroxylases
Lymphocytes, 79-6819
Poly A
Binding, 79-6807
- Dibenzo(b,def)chrysene-7,12-dione**
Hepatoma
Dose-Response Study, 79-6820
Lymphoma
Dose-Response Study, 79-6820
- Dibenzo-p-dioxin, 2,7-Dichloro-**
Acetic Acid, (2,4,5-Trichlorophenoxy)-
Environmental Hazard, 79-6774
Angiosarcoma
Carcinogenic Potential, 79-6774
Carcinogenic Potential
Mouse, Rat, 79-6774
Hemangioma
Carcinogenic Potential, 79-6774
Leukemia
Carcinogenic Potential, 79-6774
Lymphoma
Carcinogenic Potential, 79-6774
Phenol, Pentachloro-
Environmental Hazard, 79-6774
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6813
- Dibenzo-p-dioxin, 2,3,7,8-Tetrachloro-**
Aryl Hydrocarbon Hydroxylases
Lymphocytes, 79-6819
Benz(a)anthracene, 7,12-Dimethyl-
Oxidoreductases, 79-6813
Carcinoma, Epidermoid
Dose-Response Study, Rat, 79-6773
Hepatoma
Dose-Response Study, Rat, 79-6773
Hyperplasia
Epidermis, Mouse, 79-6813
Lung Neoplasms
Carcinoma, Epidermoid, 79-6773
Mouth Neoplasms
Carcinoma, Epidermoid, 79-6773
Skin Neoplasms
Antineoplastic Activity, 79-6813
Benz(a)anthracene, 7,12-Dimethyl-
79-6813
- Dibutylamine, N-Nitroso-**
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-6733
Transplacental Carcinogenesis
- Dibutylamine, N-Nitroso- (cont'd)**
Hamster, 79-6721
- Dibutyltin Diacetate**
see Stannane, Diacetoxydibutyl-
- Dibutyl Cyclic AMP**
Virus, Rous Sarcoma
Cell Transformation, Neoplastic
79-6950
- Dichromic Acid, Dipotassium Salt**
Nitric Acid, Plutonium Salt
Absorption, 79-6923
Plutonium
Absorption, 79-6923
- Dieldrin**
Perinatal Carcinogenesis
Mouse, Review, 79-6609
- Dienestrol**
Glucuronates
Metabolism, 79-6851
Gynecologic Neoplasms
Carcinoma, 79-7174
- Dienestrol, X-Hydroxy-**
Glucuronates
Metabolism, 79-6851
- Diet**
Androgens
Metabolism, Men, 79-7175
Estrogens
Metabolism, Men, 79-7175
Skin Neoplasms
Ultraviolet Rays, 79-6888
- Dietary Fats**
Adenocarcinoma
Benz(a)anthracene, 7,12-Dimethyl-
79-6817
Intestinal Neoplasms
Methane, Azoxy-, 79-6860
Sialic Acid
Metabolism, Mammary, 79-6817
- Dietary Fiber**
Dipropylamine, N-Nitroso-
Binding, 79-6694
Nitrosamines
Binding, 79-6694
Nitrous Acid, 79-6694
- Diethylamine, 2,2'-Dichloro-N-methyl-**
Structure-Activity Relationship
Mutagenic Derivatives, 79-6723
- Diethylamine, N-Nitroso-**
Acetaldehyde
Co-carcinogenic Effect, 79-6678
Alcoholic Beverages
Carcinogen Levels, 79-6722
Cell Transformation, Neoplastic
Cells, Cultured, 79-6812
Guanine, 7-Ethyl-
DNA Repair, 79-6724
Hepatoma
Hyperplasia, 79-7123
Precancerous Conditions, 79-7123
Laryngeal Neoplasms
Papilloma, 79-6725
Polyps, 79-6725
Transplacental Carcinogenesis
79-6725
Lung Neoplasms
Virus, Influenza, 79-6633
Nose Neoplasms
Transplacental Carcinogenesis
79-6725
Perinatal Carcinogenesis
Mouse, Review, 79-6609
Purine, 2-Amino-6-ethoxy-
DNA, Alkylation, 79-6862
DNA Repair, 79-6724
Liver, Rat, 79-6724, 79-6862
Respiratory Tract Neoplasms
Adenoma, 79-6678
Papilloma, 79-6678
- Diethylamine, N-Nitroso- (cont'd)**
Tracheal Neoplasms
Carcinoma, Epidermoid, 79-6725
Papilloma, 79-6725
Polyps, 79-6725
Transplacental Carcinogenesis
79-6725
- Digestive System Neoplasms**
1H-Azepine, Hexahydro-1-nitroso-
Hamster, Review, 79-6612
Azocine, Octahydro-1-nitroso-
Hamster, Review, 79-6612
Carbamic Acid, Ethylnitroso-, Ethyl Es-
ter
Histological Study, Rat, 79-6701
Morpholine, 2,6-Dimethyl-N-nitroso-
Hamster, Review, 79-6612
Vinylamine, N-Ethyl-N-nitroso-
Hamster, Review, 79-6610
- 3,3'-Dimethoxybenzidine-4,4'-diisocyanate**
see 1,1'-Biphenyl, 4,4'-Diisocyanato-
3,3'-dimethoxy-
- Dimethylamine, N-Nitroso-**
Alcoholic Beverages
Carcinogen Levels, 79-6722
Body Fluids
Quantitation Method, 79-6734
DNA Replication
Liver Regeneration, 79-6864
Enzyme Activation
Transplacental Carcinogenesis, Review
79-6608
Guanine, 7-Methyl-
Neuroglia, 79-6704
Hepatoma
Cell Division, 79-6864
Kidney Neoplasms
Adenoma, 79-6863
Age Factors, Rat, 79-6863
Carcinoma, 79-6863
Fibroma, 79-6863
Mesenchymoma, 79-6863
Lactate Dehydrogenase
Lung, Mouse, 79-6698
Methylation
Brain, Rat, 79-6704
Microsomes, Liver
Quantitation Method, 79-6734
Nephroblastoma
Age Factors, Rat, 79-6863
Purine, 2-Amino-6-methoxy-
Neuroglia, 79-6704
Transplacental Carcinogenesis
Hamster, 79-6721
- Diphenylamine, N-Nitroso-**
Hepatoma
Dose-Response Study, 79-6730
Lung Neoplasms
Adenoma, 79-6730
- Dipropylamine, 2-Acetoxy-N-nitroso-**
Pancreatic Neoplasms
Precancerous Conditions, 79-7125
- Dipropylamine, 2,2'-Dihydroxy-N-nitroso-**
Pancreatic Juice
Metabolism, Hamster, Rat, 79-6726
Pancreatic Neoplasms
Bile Acids and Salts, 79-6727
Precancerous Conditions, 79-7125
Transplacental Carcinogenesis
Hamster, 79-6721
- Dipropylamine, 2,2'-Dioxo-N-nitroso-**
Pancreatic Neoplasms
Adenocarcinoma, 79-6728
Transplantation, Homologous, 79-6728
- Dipropylamine, 2-Hydroxy-N-nitroso-2'-oxy-**
Pancreatic Juice
Metabolism, Hamster, Rat, 79-6726
- Dipropylamine, N-Nitroso-**
Dietary Fiber

Dipropylamine, *N*-Nitroso-(cont'd)
 Binding, 79-6694
 Food Contamination
 Quantitation Method, 79-6729
 Transplacental Carcinogenesis
 Hamster, 79-6721

Dipyrido(1,2-*a*:2',1'-*c*)pyrazinedium, 6,7-Dihydro-
 Ames Test
 Mutagenic Activity, 79-6758
Aspergillus nidulans
 Mutagenic Activity, 79-6758

Dipyrido(1,2-*a*:3',2'-*d*)imidazole, 2-Amino-6-methyl-
 Cell Transformation, Neoplastic
 Dose-Response Study, 79-6737

Diquat
see Dipyrido(1,2-*a*:2',1'-*c*)pyrazinedium, 6,7-Dihydro-

Disgerminoma
 Neoplasms, Multiple Primary
 Radiation, Ionizing, 79-6913
 Testicular Neoplasms
 Histocompatibility Antigens, 79-7098

DNA
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Nucleic Acid Denaturation, 79-6691
 Bleomycin
 Double Strand Breaks, 79-6904
 Carcinogen, Chemical
 Spectrum Analysis, Raman, Review
 79-6606
 Hydroxylamine, *N*-Fluoren-2-yl-
 Nucleic Acid Denaturation, 79-6691
 Radiation, Ionizing
 Double Strand Breaks, 79-6904

DNA, Circular
 Virus, Rous Sarcoma
 DNA Replication, 79-6944

DNA, Neoplasm
 Astrocytoma
 DNA-RNA Hybridization, 79-7190
 Glioblastoma Multiforme
 DNA-RNA Hybridization, 79-7190

DNA Photolyase
 Ultraviolet Rays
 Cell Transformation, Neoplastic
 79-6874
 DNA Repair, 79-6874

DNA Polymerase
 Virus, Avian Leukosis
 Antigenic Determinants, 79-6956
 Virus, Pheasant RNA Tumor
 Antigenic Determinants, 79-6956
 Radioimmunoassay, 79-6956

DNA Repair
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Fibroblasts, 79-6873
 Nucleotides, 79-6873
 Anemia, Aplastic
 Ultraviolet Rays, 79-6890
 Benz(a)anthracene, 7-Bromo-methyl-12-methyl-
 DNA Adducts, 79-6805
 Benz(a)anthracene, 7-Bromomethyl-
 DNA Adducts, 79-6805
 Carcinogen, Chemical
 Cell Transformation, Neoplastic, Review, 79-6626
 Diethylamine, *N*-Nitroso-
 Guanine, 7-Ethyl-, 79-6724
 Purine, 2-Amino-6-ethoxy-, 79-6724
 Glycine, *N*-(Aminocarbonyl)-*N*-nitroso-
 Mutation, 79-6706
 L Cells
 Benz(a)anthracene, 7-Bromo-methyl-
 12-methyl-, 79-6805
 Benz(a)anthracene, 7-Bromomethyl-

DNA Repair (cont'd)
 Benz(a)anthracene, 7-Bromomethyl-
 79-6805
 Leukemia L1210
 Radiation, Ionizing, 79-6904
 Mutagens
 Peptide Hydrolases, Review, 79-6623
 Oncogenic Viruses
 Peptide Hydrolases, Review, 79-6623
 Propane, 1,2-Dibromo-3-chloro-
 Germ Cells, Mouse, 79-6668
 Radiation, Ionizing
 Chromosome Aberrations, 79-6629
 Skin Neoplasms
 Fibroblasts, 79-6875
 Ultraviolet Rays
 Azaguanine, Thioguanine Resistance
 79-6877
 Caffeine, 79-6876
 Cell Transformation, Neoplastic, Review, 79-6626
 Chloramphenicol, 79-6622
 Culture Media, 79-6870
 DNA Photolyase, 79-6874
 Fibroblasts, 79-6873, 79-6877, 79-6890
 Mutagenic Activity, Review, 79-6625
 Mutagenic, Carcinogenic Activity, Review, 79-6622, 79-6623
 Nucleotides, 79-6873
 Peptide Hydrolases, Review, 79-6623
 Urea, Methyl Nitroso-
 Brain, Liver, 79-6709
 Liver, Rat, 79-6705
 Xeroderma Pigmentosum
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-, 79-6873
 Complementation Group, 79-6875
 Fibroblasts, 79-6875
 Radiation, Ionizing, 79-6629
 Ultraviolet Rays, 79-6629, 79-6873
 79-6875, 79-6877, 79-6890

DNA Replication
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Liver Regeneration, 79-6864
 Benz(a)anthracene, 7,12-Dimethyl-
 Liver Regeneration, 79-6864
 Dimethylamine, *N*-Nitroso-
 Liver Regeneration, 79-6864
 L Cells
 Tannic Acid, 79-6786
 Mammary Neoplasms, Experimental
 Tannic Acid, 79-6786
 2-Propenoic Acid, 3-(5-Nitro-2-furyl)-
 Fibroblasts, 79-6697
 Tannic Acid
 Inhibitory Factor, 79-6786
 Lymphocytes, 79-6786
 12-*O*-Tetradecanoylphorbol-13-acetate
 Cells, Cultured, 79-6793
 Ultraviolet Rays
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6871
 Cell Cycle Kinetics, 79-6870
 Contact Inhibition, 79-6870
 Urea, Methyl Nitroso-
 Deoxyribonucleosides, 79-6705
 Virus, Epstein-Barr
 Deoxyribonuclease, 79-7014
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-7017
 Virus, Herpes Simplex 1
 Ribonucleotides, 79-7006
 Virus, Moloney Murine Leukemia
 RNA, Viral, 79-6984
 Virus, Rous Sarcoma
 DNA, Circular, 79-6944
 RNA Polymerase, 79-6938

DNA Restriction Enzyme
 Virus, Adeno 12
 DNA-RNA Hybridization, 79-7046
 Virus, Harvey Murine Sarcoma-Leukemia
 Cleavage Sites, 79-6982
 Virus, Polyoma
 Deletion Mutants, 79-7026
 Virus, SV40

DNA Restriction Enzyme (cont'd)
 Chromosome Analysis, 79-6634
 Transformation, Genetic, Review
 79-6634

DNA, Viral
 Paraganglioma
 Virus, Papova, 79-7020
 Virus, Adeno 12
 Antigens, Neoplasm, 79-7050
 Antigens, Viral, 79-7050
 Cell Transformation, Neoplastic
 79-7046, 79-7048
 Deletion Mutants, 79-7050
 Virus, Bovine Papilloma
 Cleavage Sites, 79-6998
 Endonucleases, 79-6998
 Nucleotide Sequence, 79-6996
 Virus, Harvey Murine Sarcoma-Leukemia
 Transformation, Genetic, 79-6982
 Virus, Murine Mammary Tumor
 Endonucleases, 79-6961
 Vertical Transmission, 79-6961
 Virus, Papilloma
 Nucleotide Sequence, 79-6996
 Virus, Polyoma
 Antigens, Neoplasm, 79-7021
 Binding Sites, 79-7025
 Deletion Mutants, 79-7021, 79-7023
 Nucleic Acid Conformation, 79-7022
 Nucleotide Sequence, 79-7024
 RNA, Messenger, 79-7024
 Virus, Polyoma, BK
 Nucleotide Sequence, 79-7031
 Virus, Rous Sarcoma
 Virus Rescue, 79-6946
 Virus, Shope Rabbit Papilloma
 Nucleotide Sequence, 79-6996
 Virus, Stump-Tailed Macaque
 Nucleotide Sequence, 79-7003
 Virus, SV40
 Mutation, Review, 79-6634

L-Dopa
see Alanine, 3-(3,4-Dihydroxyphenyl)-

Drosophila melanogaster
 Microwaves
 Mutagenic Activity, 79-6895

Drug Therapy
 Leukemia
 Multiple Myeloma, 79-7155
 Leukemia, Myeloblastic
 Neoplasms, Multiple Primary, 79-7105
 Sarcoma, Osteogenic
 Multiple Myeloma, 79-6908

Dwarfism
 Leukemia, Lymphoblastic
 Case Report, 79-7109

Ear Neoplasms
 Carcinoma, Epidermoid
 Benzenamine, *N*-Hydroxy-*N*-nitroso-,
 Ammonium Salt, 79-6754
 1,1'-Biphenyl, 4,4'-Diisocyanato-
 3,3'-dimethoxy-, 79-6769
p-Toluidine, *N*-Isopropyl- α -(2-
 methylhydrazino)-, 79-6750
 Cholangioma
 Benzenamine, 2-Methoxy-5-methyl-
 79-6755
 Neurilemmoma
 Radiation, Ionizing, 79-6901

Endometrial Hyperplasia
 Uterine Neoplasms
 Progesterational Hormones, 79-7173

Endometriosis
 Adenocarcinoma
 Case Report, 79-6854
 Ovarian Neoplasms
 Adenocarcinoma, 79-7133
 Adenocarcinoma, Papillary, 79-7133

Endonucleases
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

- Endonucleases (cont'd)**
 Guanosine, 2'-Deoxy-, 79-6691
 Hydroxylamine, *N*-Fluoren-2-yl-
 Guanosine, 2'-Deoxy-, 79-6691
 Virus, Bovine Papilloma
 DNA, Viral, 79-6998
 Virus, Murine Mammary Tumor
 DNA, Viral, 79-6961
- Enovid**
 Uterine Neoplasms
 Adenocarcinoma, 79-6854
- Environmental Hazard**
 Acetic Acid, (2,4,5-Trichlorophenoxy)-
 Dibenzo-*p*-dioxin, 2,7-Dichloro-
 79-6774
 Nasopharyngeal Neoplasms
 Epidemiology, Taiwan, 79-7141
 Phenol, Pentachloro-
 Dibenzo-*p*-dioxin, 2,7-Dichloro-
 79-6774
- Eosinophilia**
 Leukemia, Myelocytic
 Case Report, 79-7108
 Karyotyping, 79-7108
- Ependyoma**
 Nitrous Acid, Sodium Salt
 Mercury, Chloromethyl-, 79-6651
 Urea, Ethyl Nitroso-
 Mercury, Chloromethyl-, 79-6651
- Epidermal Growth Factors**
see Peptides
- Epidermodysplasia Verruciformis**
 Carcinoma, Epidermoid
 Case Report, 79-7030
 Skin Neoplasms
 Case Report, 79-7030
- Epoxide Hydratases**
 Hyperplasia
 Endoplasmic Reticulum, 79-6684
 Liver Neoplasms
 Hyperplasia, 79-6684
- Erythema**
 Teleocidin B, Dihydro
 Case Report, 79-6911
 Ultraviolet Rays
 Carcinogenic Potential, 79-6882
- Erythrocebus patas**
 Urea, Ethyl Nitroso-
 Maternal-Fetal Exchange, 79-6716
- Erythrocytes**
 Cadmium Chloride
 Metalloproteins, 79-6645
- Erythroleukemia**
 Dihydroteleocidin B
 Cell Differentiation, 79-6844
 Virus, Moloney Murine Sarcoma
 Anti-Antibodies, 79-6988
- Erythropoiesis**
 Radiation, Ionizing
 Bone Marrow, Spleen, 79-6914
- Escherichia coli**
 Glycine, *N*-(Aminocarbonyl)-*N*-nitroso-
 Mutation, 79-6706
 Liver Neoplasms
 Mouse, 79-6643
 Nitrosamines
 Mutagenic Activity, 79-6732
- Esophageal Neoplasms**
 Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-
 furyl)-
 Dose-Response Study, Hamster
 79-6690
 Alcoholic Beverages
 Epidemiology, France, 79-6722
 Carcinoma, Epidermoid
 Carbamic Acid, Diethyldithio-, 2-
 Chloroallyl Ester, 79-6702
 Epidemiology
- Esophageal Neoplasms (cont'd)**
 Greenland, 79-7151
Fusarium
 Epidemiology, Transkei, 79-7182
 Papilloma
 Carbamic Acid, Diethyldithio-, 2-
 Chloroallyl Ester, 79-6702
 Zeaxaralene
 Food Contamination, 79-7182
- Esterases**
 Acetic Acid, Methylnitrosaminomethyl
 Ester
 Metabolism, Rat, 79-6865
- Estradiol**
 Aryl Hydrocarbon Hydroxylases
 Lymphocytes, 79-6819
 Gynecologic Neoplasms
 Precancerous Conditions, 79-6852
 Hyperplasia
 Retinol Acetate, 79-6853
 4,4'-Stilbenediol, α, α' -Diethyl-
 Antigens, 79-6852
 Testicular Neoplasms
 Leydig Cell Tumor, 79-7137
 Vaginal Neoplasms
 Hyperplasia, 79-6853
 Precancerous Conditions, 79-6853
 Testosterone, Propionate, 79-6853
- Estradiol, 17-Ethynyl-**
 Chromatids
 Lymphocytes, 79-6856
 Mutagenic Activity, 79-6856
- Estrogens**
 Diet
 Metabolism, Men, 79-7175
 Mammary Neoplasms, Experimental
 Receptors, Hormone, 79-6858
 Perinatal Carcinogenesis
 Species Difference, Review, 79-6602
 Uterine Neoplasms
 Adenocarcinoma, 79-7173
 Epidemiology, 79-7171, 79-7173
- Ethane, Bromo-**
 Microsomes, Liver
 Macromolecules, Binding, 79-6664
- Ethane, 1,2-Dibromo-**
 Microsomes, Liver
 Macromolecules, Binding, 79-6664
 Stomach Neoplasms
 Carcinogenic Activity, Mouse, 79-6666
- Ethane, 1,1-Dichloro-2,2-bis(*p*-
 ethylphenyl)-**
 Hepatoma
 Dose-Response Study, 79-6665
 Liver Neoplasms
 Adenoma, 79-6665
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-
 chlorophenyl)-**
 Perinatal Carcinogenesis
 Mouse, Review, 79-6609
- Ethanol, 2-Bromo-**
 Microsomes, Liver
 Macromolecules, Binding, 79-6664
- Ethanol, *N*-Nitrosoiminodi-**
 Ames Test
 Dose-Response Study, 79-6695
 Body Fluids
 Quantitation Method, 79-6734
 Microsomes, Liver
 Quantitation Method, 79-6734
 Respiratory Tract Neoplasms
 Carcinoma, 79-6611
 Papilloma, 79-6611
 Urine
 Adsorption, Skin, 79-6696
- Ether, Bis(2-chloroethyl)-**
 Acetaldehyde, Chloro-
 Hepatocarcinogenesis, 79-6739
 Acetic Acid, Thiodi-
- Ether, Bis(2-chloroethyl)-(cont'd)**
 Urinary Metabolites, 79-6739
 Alanine, 3-((Carboxymethyl)thio)-
 Urinary Metabolites, 79-6739
- Ethyl Alcohol**
 Anemia, Aplastic
 Sister-Chromatid Exchange, 79-6661
 1-Anthracenamide
 Emission Spectra, 79-6761
 2-Anthracenamide
 Emission Spectra, 79-6761
 Laryngeal Neoplasms
 Epidemiology, 79-7181
 Mouth Neoplasms
 Carcinoma, Epidermoid, 79-6640
 Pharyngeal Neoplasms
 Carcinoma, Epidermoid, 79-6640
- Ethylene, 1-Bromo-2-*p*-(ethylphenyl)-1,2-
 diphenyl-**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6667
- Ethylene, Chloro-**
 Chromatids
 Mutagenic Activity, 79-6662
 Chromosome Aberrations
 Lymphocytes, 79-6662
 Occupational Hazard, 79-6662
 Skin Diseases
 Histopathological Study, 79-6663
 Occupational Hazard, 79-6663
- Ethylene, 1,1-Dichloro-**
 Skin Neoplasms
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6666
- Etiocolanolone**
 Breast Neoplasms
 Urine, 79-7150
- Eye Neoplasms**
 Adenoma
 Benzenamine, *N*-Hydroxy-*N*-nitroso-,
 Ammonium Salt, 79-6754
 Tellurium, Tetrakis(diethyldithiocar-
 bamato)-, 79-6658
 Light
 Transplantation, Homologous, 79-6894
 Neuroepithelioma
 Urea, Ethyl Nitroso-, 79-6715
- Fatty Acids**
 Virus, Kirsten Murine Sarcoma
 Cell Transformation, Neoplastic
 79-6841
- Fenaminosulf**
see Benzenediazolsulfonic Acid, *p*-
 -(Dimethylamino)-, Sodium Salt
- Fenthion**
 Fibrosarcoma
 Dose-Response Study, 79-6654
 Rhabdomyosarcoma
 Dose-Response Study, 79-6654
 Sarcoma
 Dose-Response Study, 79-6654
 Testicular Neoplasms
 Leydig Cell Tumor, 79-6654
- Fibroblasts**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-
 yl-
 DNA Repair, 79-6873
 Butane, 1,2:3,4-Diepoxy-
 Chromosome Aberrations, 79-6670
 Cell Transformation, Neoplastic
 Interferon, 79-6983
 Mesenchymoma
 Cell Adhesion, 79-7118
 Hematopoiesis, 79-7118
 2-Propenoic Acid, 3-(5-Nitro-2-furyl)-
 DNA Replication, 79-6697
 Skin Neoplasms
 DNA Repair, 79-6875
 12-*O*-Tetradecanoylphorbol-13-acetate

- Fibroblasts (cont'd)**
Clostridiopeptidase A, 79-6795
Ultraviolet Rays
DNA Repair, 79-6873, 79-6877
79-6890
Xeroderma Pigmentosum
DNA Repair, 79-6875
- Fibroma**
Kidney Neoplasms
Dimethylamine, *N*-Nitroso-, 79-6863
o-Toluidine, Hydrochloride
Carcinogenic Potential, 79-6752
- Fibronectins**
see Membrane Proteins
- Fibrosarcoma**
Abdominal Neoplasms
Azobenzene, 79-6766
Brain Neoplasms
Radiation, Ionizing, 79-6902
Cholanthrene, 3-Methyl-
Corynebacterium parvum, 79-6907
Radiation, Ionizing, 79-6907
Cortisol Acetate
Neoplasm Metastasis, 79-7083
Fenthion
Dose-Response Study, 79-6654
Heart Neoplasms
Virus, DNA Tumor, 79-7051
Mandibular Neoplasms
Radiation, Ionizing, 79-6909
Radiation, Ionizing
Case Report, 79-6909
Neoplasm Metastasis, 79-7083
Neoplasm Recurrence, 79-6907
Transplantation Immunology, 79-6907
Tracheal Neoplasms
Carcinoma, 79-6824, 79-6825
Cholanthrene, 3-Methyl-, 79-6824
79-6825
Ultraviolet Rays
Dose-Response Study, 79-6882
Transplantation Immunology, 79-6887
Virus, Friend Murine Leukemia
Antigens, Neoplasm, 79-6977
Antigens, Viral, 79-6977
Histocompatibility Antigens, 79-6977
Virus, Herpes Simplex 2
Antigens, Viral, 79-7007
Virus, SV40
Deletion Mutants, 79-7036
- Fluoranthene**
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 79-6815
- Fluoren-2-amine**
Microsomes, Liver
Ames Test, 79-6842
Retinol
Ames Test, 79-6842
- Food Additives**
Transplacental Carcinogenesis
Bioassays, Review, 79-6620
- Food Contamination**
Aniline, Dinitro- (Mixed Isomers)
Nitrosamines, 79-6729
Anisole, *p*-Allyl-
Carcinogenic Potential, Review
79-6614
Benzene, 4-Allyl-1,2-(methylenedioxy)-
Carcinogenic Potential, Review
79-6614
Benzene, 1,2,4-Trimethoxy-5-(1-propenyl)-
Carcinogenic Potential, Review
79-6614
Benzo(a)pyrene
Metabolism, 79-6836
Quantitation, 79-6840
Butylamine, *N*-Ethyl-*N*-nitroso-
Quantitation Method, 79-6729
Dipropylamine, *N*-Nitroso-
Quantitation Method, 79-6729
- Food Contamination (cont'd)**
Esophageal Neoplasms
Zearalenone, 79-7182
Hexane, 1-Nitro-
Nitrous Acid, 79-6693
Quantitation Method, 79-6693
- Foreign Bodies**
Cell Transformation, Neoplastic
Abnormal Film Matrix, Review
79-6632
- Formaldehyde**
Phenethylamine, *N*, α -Dimethyl-*N*-nitroso-
Microsomes, Liver, 79-6742
Phenethylamine, *N*-Methyl-*N*-nitroso-
Barbituric Acid, 5-Ethyl-5-phenyl-, 79-6742
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-**
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-6733
- Fusarium**
Esophageal Neoplasms
Epidemiology, Transkei, 79-7182
- Gallbladder Neoplasms**
Carcinoma
Aflatoxin B1, 79-6790
- Gamma Globulins**
Sarcoma
Benzo(a)pyrene, 79-6839
- Ganglioneuroma**
Adrenal Gland Neoplasms
Benzenamine, *N*-Hydroxy-*N*-nitroso-, Ammonium Salt, 79-6754
Brain Neoplasms
Urea, Ethyl Nitroso-, 79-6715
- Gastrectomy**
Stomach Neoplasms
Adenocarcinoma, 79-7129
Bile Reflux, 79-7170
Carcinoma, 79-7129
Epidemiology, 79-7170
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 79-7129
- Gastrointestinal Neoplasms**
Adenocarcinoma
Genetics, Rat, 79-7131
Peutz-Jeghers Syndrome, 79-7130
Carcinoma
Peutz-Jeghers Syndrome, 79-7130
Cholanthrene, 3-Methyl-
Animal Model, Hamster, 79-6822
Polyps
Genetics, 79-7130
- Gastrointestinal System**
Plutonium
Absorption, 79-6923
Adsorption, 79-6924
- Genetics**
Bladder Neoplasms
Carcinoma, Transitional Cell, 79-7132
Breast Neoplasms
Case Report, 79-7134
Carcinoma, Transitional Cell
Case Report, 79-7132
Gastrointestinal Neoplasms
Polyps, 79-7130
Gynecologic Neoplasms
Risk Factors, 79-7134
Kidney Neoplasms
Adenocarcinoma, 79-7127
Melanoma
Immune Response, 79-7086
Ovarian Neoplasms
Adenocarcinoma, 79-7133
Retinoblastoma
Age Factors, 79-7100
Bilateral Tumor, 79-7100
Sarcoma, Osteogenic
- Genetics (cont'd)**
Case Report, 79-7116
Skin Neoplasms
Virus, Papilloma, 79-7030
- Gentamicin**
Benz(a)anthracene, 7,12-Dimethyl-
Cell Transformation, Neoplastic
79-6823
Cholanthrene, 3-Methyl-
Cell Transformation, Neoplastic
79-6823
Radiation, Ionizing
Cell Transformation, Neoplastic
79-6823
- Giant Cell Tumors**
Petroleum
Immune Response, Hamster, 79-6672
- Glioblastoma Multiforme**
DNA, Neoplasm
DNA-RNA Hybridization, 79-7190
Virus, SV40
Antigens, Neoplasm, 79-7037
Virus-Like Particles, 79-7037
- Glioma**
Benzenamine, *N*-Hydroxy-*N*-nitroso-, Ammonium Salt
Dose-Response Study, 79-6754
Urea, Ethyl Nitroso-
Transplacental Carcinogenesis, Review
79-6607, 79-6608
Virus, Simian Sarcoma
Virus Replication, 79-7004
- Glomerulonephritis**
Virus, Murine Leukemia
Autoantibodies, 79-7097
- Glucocorticoids**
Mammary Neoplasms, Experimental
Precancerous Conditions, 79-6963
Virus, Murine Mammary Tumor
79-6963
Virus, Murine Mammary Tumor
RNA, Viral, 79-6963
- Glucose, 2-Deoxy-**
Virus, Rous Sarcoma
Viral Proteins, 79-6941
- Glucosephosphate Dehydrogenase**
Acetamide, *N*-Fluoren-2-yl-
Enzymatic Activity, 79-6682
- Glucuronidase**
4-Biphenylamine
Ames Test, 79-6768
Laryngeal Neoplasms
Neutrophils, 79-7090
Precancerous Conditions, 79-7090
- Glutamic Acid**
Cell Transformation, Neoplastic
Pyrolysis Product, 79-6737
- Glutamyltranspeptidase**
Serine, Diazoacetate (Ester)
Choline, 79-6683
- Glutathione Reductase**
Nephroblastoma
Chromosomes, Human, 6-12, 79-7126
- Glycine, *N*-Amidino-**
Glycine, *N*-(Aminocarbonyl)-*N*-nitroso-
Nitrosation, 79-6706
- Glycine, *N*-(Aminocarbonyl)-*N*-nitroso-**
DNA Repair
Mutation, 79-6706
Escherichia coli
Mutation, 79-6706
Glycine, *N*-Amidino-
Nitrosation, 79-6706
Mutation
DNA Repair, 79-6706
- Glycoproteins**
Virus, Rauscher Murine Leukemia

Glycoproteins (cont'd)
Binding Sites, 79-6992
Cell Membrane, 79-6992

Gonadotropins
Benz(a)anthracene, 7,12-Dimethyl-
Estrus, Rat, 79-6811
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-
79-6811

Gonadotropins, Chorionic
Choriocarcinoma
Isolation and Characterization
79-7189

Graft vs Host Reaction
T-Lymphocytes
Age Factors, Hamster, 79-7064
Melanoma
Transplantation, Homologous, 79-7089
Neoplasms, Experimental
Virus, Adeno 2, 79-7064

Graft Rejection
Teratoid Tumor
Histocompatibility Antigens, 79-7079

Granulocytes
Leukemia, Myeloblastic
Cell Differentiation, 79-7193
Leukemia, Myelocytic
Cell Differentiation, 79-7073
Macrophages
Contact Inhibition, 79-7193
Prostaglandins E
Colony Stimulating Factor, 79-7073
Virus, Friend Murine Leukemia
Cell Differentiation, 79-7073

Griseofulvin
Ames Test
Mutagenic Activity, 79-6785
Chromosome Aberrations
Bone Marrow, 79-6785

Growth
Breast Neoplasms
Insulin, 79-7200
Carcinoma, Ehrlich Tumor
Radiation, Ionizing, 79-6906
Hepatoma
Macrophages, 79-7081
Neoplasms, Experimental
Concanavalin A, 79-7080
Retinal
Cells, Cultured, 79-6843
Retinoic Acid
Cells, Cultured, 79-6843
Retinol
Cells, Cultured, 79-6843
Retinol Acetate
Cells, Cultured, 79-6843
Sarcoma
T-Lymphocytes, 79-7082
Sarcoma, Yoshida
Macrophages, 79-7081

Growth Substances
Cell Transformation, Neoplastic
Peptides, 79-7187

Guanidine, 1-Methyl-3-nitro-1-nitroso-
Adenocarcinoma
Cyclophosphamide, 79-6866
Chromosome Aberrations
Quantitation Method, 79-6744
Mutagenic Activity
Thioguanine Resistance, 79-6700
Mutation
Colony Formation, 79-7044
Stomach Neoplasms
Adenocarcinoma, 79-6866
Cells, Cultured, 79-6866
Gastrectomy, 79-7129

Guanine, 7-Ethyl-
Diethylamine, *N*-Nitroso-

Guanine, 7-Ethyl- (cont'd)
DNA Repair, 79-6724

Guanine, 7-Methyl-
Acetic Acid, Methylnitrosaminomethyl
Ester
Organ Specificity, 79-6865
Dimethylamine, *N*-Nitroso-
Neuroglia, 79-6704
Triazene, 3,3-Dimethyl-1-phenyl-
Perinatal Carcinogenesis, 79-6709
Urea, Methyl Nitroso-
Neurons, 79-6704
Perinatal Carcinogenesis, 79-6709

Guanosine
Carcinogen, Chemical
Benzylation, 79-6740

Guanosine, 2'-Deoxy-
Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-
yl-
Endonucleases, 79-6691
Hydroxylamine, *N*-Fluoren-2-yl-
Endonucleases, 79-6691

Guthion
Pancreatic Neoplasms
Islet Cell Tumor, 79-6777
Thyroid Neoplasms
Carcinogenic Potential, 79-6777

Gynecologic Neoplasms
Adenoma
1,5-Naphthalenediamine, 79-6772
Benz(a)anthracene, 7,12-Dimethyl-
Hormone Imbalance, 79-6850
Carcinoma
Dieneol, 79-7174
Phenol, 4,4'-(1,2-Diethylene)di-, *meso*-
79-7174
4,4'-Stilbenediol, α,α' -Diethyl-
79-7174
Estradiol
Precancerous Conditions, 79-6852
Genetics
Risk Factors, 79-7134
Intestinal Neoplasms
Radiotherapy, 79-6917
Marital Status
Epidemiology, 79-7178
Nervous System Neoplasms
Urea, Ethyl Nitroso-, 79-6703
Polyps
1,5-Naphthalenediamine, 79-6772
Sarcoma
1,5-Naphthalenediamine, 79-6772
4,4'-Stilbenediol, α,α' -Diethyl-
Co-carcinogenic Effect, 79-6850
Precancerous Conditions, 79-6852
Transplacental Carcinogenesis
79-6703, 79-6846

Hair Dyes
Breast Neoplasms
Epidemiology, 79-7156
Uterine Neoplasms
Epidemiology, 79-7156

Haptens
Virus, Epstein-Barr
Anti-Antibodies, 79-7015

Haworthia mirabilis
Plant Tumors
Radiation, Ionizing, 79-6898

Heart Neoplasms
Fibrosarcoma
Virus, DNA Tumor, 79-7051

Heat
Carcinoma, Epidermoid
Keratinosis, 79-6911

HeLa Cells
12-*O*-Tetradecanoylphorbol-13-acetate
Peptides, 79-6799
Ultraviolet Rays
Benz(a)anthracene, 7,12-Dimethyl-
79-6871

HeLa Cells (cont'd)
Cell Survival, 79-6871
Virus, Simian Sarcoma
Virus Replication, 79-7004

Heliotrine
Ames Test
S9 Fraction, 79-6776

Hemangioblastoma
Neoplasms, Multiple Primary
Hippel-Lindau Disease, 79-7124

Hemangioendothelioma
Aflatoxin B1
Pancreatic Neoplasms, 79-6790
Liver Neoplasms
Thorium Dioxide, 79-6770
Thorium Dioxide
Case Report, 79-6770

Hemangioma
Carcinoma, Basal Cell
Radiotherapy, 79-6905
Dibenzo-*p*-dioxin, 2,7-Dichloro-
Carcinogenic Potential, 79-6774
Splenic Neoplasms
Phosphamidon, 79-6655

Hemangiopericytoma
Splenic Neoplasms
Azobenzene, 79-6766

Hematologic Diseases
Sarcoma Kaposi's
Case Report, 79-7114

Hematopoiesis
Mesenchymoma
Fibroblasts, 79-7118
Myelofibrosis
Transplantation Model, 79-7118
Myeloproliferative Disorders
Transplantation Model, 79-7118
Pancreatic Neoplasms
Pentadecane, 2,6,10,14-Tetramethyl-
79-6672

Hematopoietic Stem Cells
Radiation, Ionizing
Blood Cell Count, 79-6914
Virus, Abelson Murine Leukemia
Antigens, Viral, 79-6974
Virus, Avian Leukemia
Bone Marrow, 79-6929
Cell Transformation, Neoplastic
79-6928, 79-6929
Replication-Defective Mutants
79-6929

Hemophilia
Neoplasms
Epidemiology, 79-7172

Hepatoma
Acetamide, *N*-Fluoren-2-yl-
Chromosomal Proteins, Non-Histone
79-7122
Hyperplasia, 79-7123
Precancerous Conditions, 79-7123
Acetanilide, 4'-(*p*-Fluorophenyl)-
Acetic Acid, Lead Salt, 79-6689
Adenoma
1,5-Naphthalenediamine, 79-6772
Aflatoxin B1
Carcinogenic Activity, Monkey
79-6790
Alpha Fetoproteins
RNA, Messenger, 79-7094
Anthraquinone, 1-Amino-2-methyl-
Dose-Response Study, 79-6792
Australia Antigen
Ultrastructural Study, 79-7063
Benz(a)anthracene, 7,12-Dimethyl-
DNA Adducts, 79-6804
Toxic Metabolites, 79-6804
Benzenamine, *N*-Hydroxy-*N*-nitroso-,
Ammonium Salt

Hepatoma (cont'd)

- Dose-Response Study, 79-6754
- Benzenamine, 2-Methoxy-5-methyl-
Dose-Response Study, 79-6755
- Benzene, 4-Allyl-1,2-(methylenedioxy)-
Neoplasm Metastasis, 79-6748
- 1,3-Benzodioxole, 5-(2-(Octylsulfinyl)propyl)-
Carcinogenic Potential, 79-6760
- 7,8-Benzoflavone
Toxic Metabolites, 79-6804
- p*-Benzoquinone Dioxime
Dose-Response Study, 79-6763
- Carbamic Acid, Diethyldithio-, 2-Chloroallyl Ester
Carcinogenic Potential, 79-6702
- Dibenzo(b,def)chrysene-7,12-dione
Dose-Response Study, 79-6820
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Dose-Response Study, Rat, 79-6773
- Diethylamine, *N*-Nitroso-
Hyperplasia, 79-7123
- Precancerous Conditions, 79-7123
- Dimethylamine, *N*-Nitroso-
Cell Division, 79-6864
- Diphenylamine, *N*-Nitroso-
Dose-Response Study, 79-6730
- DNA Adducts
Epithelial Cells, Liver, 79-6804
- Ethane, 1,1-Dichloro-2,2-bis(*p*-ethylphenyl)-
Dose-Response Study, 79-6665
- Growth
Chromosomal Proteins, Non-Histone
79-7122
- Hycanthone Methanesulfonate
Carcinogenic Potential, Mouse
79-6779
- 1,2-Hydrazinedicarbothioamide
Dose-Response Study, 79-6717
- Hyperplasia
Kepone, 79-6782
- Kepone
Carcinogenic Activity, Rat, 79-6782
- Macrophages
Chemotaxis Inhibitor, 79-7095
- Growth, 79-7081
- 2-Naphthylamine
Cyclophosphamide, 79-6771
- Petroleum
Immune Response, Hamster, 79-6672
- Phenol, 2,4,6-Trichloro-
Dose-Response Study, 79-6747
- p*-Phenylenediamine, 2-Chloro-, Sulfate
Carcinogenic Potential, 79-6759
- Stannane, Diacetoxydiethyl-
Dose-Response Study, 79-6775
- Terephthalic Acid, Dimethyl Ester
Carcinogenic Potential, 79-6749
- Thiophene, 2,5-Dihydro-, 1,1-Dioxide
Dose-Response Study, 79-6778
- o*-Toluidine, 5-Chloro-
Dose-Response Study, 79-6751
- Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-
Dose-Response Study, 79-6713
- Virus, Hepatitis
Antigens, Viral, 79-7063
- Virus, Lactate Dehydrogenase
Macrophages, 79-7095
- 3-Heptanone, 6-(Dimethylamino)-4,4-diphenyl-, Hydrochloride
Chromosome Aberrations
Spermatozoa, 79-6671
- Sex Chromosomes
Mutagenic Activity, Mouse, 79-6671

Hexane, 1-Nitro-

- Food Contamination
Quantitation Method, 79-6693
- Nitrous Acid
Food Contamination, 79-6693

Hippel-Lindau Disease

- Hemangioblastoma
Neoplasms, Multiple Primary, 79-7124
- Islet Cell Tumor
Case Report, 79-7124

Hippel-Lindau Disease (cont'd)

- Pheochromocytoma
Neoplasms, Multiple Primary, 79-7124

Histiocytoma

- Neurofibromatosis
Case Report, 79-7104

Histocompatibility Antigens

- Fibrosarcoma
Virus, Friend Murine Leukemia
79-6977
- Hybrid Cells
Transplantation Immunology, 79-7071
- L Cells
Hybrid Cells, 79-7092
- Leukemia
Transplantation Immunology, 79-6878
- Lung Neoplasms
Asbestosis, 79-6650
- Lymphoma
Hybrid Cells, 79-7071
- Mammary Neoplasms, Experimental
Hybrid Cells, 79-7071, 79-7092
- Pulmonary Fibrosis
Asbestos, 79-6650
- Sarcoma
Virus, SV40, 79-7040
- Teratoid Tumor
Chromosomes, 79-7079
- Graft Rejection, 79-7079
- Testicular Neoplasms
Disgerminoma, 79-7098
- Teratoid Tumor, 79-7098
- Virus, Adeno 12
Cell Transformation, Neoplastic
79-7048
- Transplantation Immunology, 79-7049
- Virus, CEL0
Genes, Viral, 79-7059
- Virus, Gross Murine Leukemia
T-Lymphocytes, 79-6980
- Virus, Rauscher Murine Leukemia
T-Lymphocytes, 79-6991
- Viral Proteins, 79-6991
- Virus, SV40
Immunogenetics, 79-7040
- Transplantation Immunology, 79-7040

Histones

- RNA, Messenger
Poly A, 79-7191

Hodgkin's Disease

- Adenocarcinoma
Immunologic Deficiency Syndromes
79-7088
- Age Factors
Epidemiology, 79-7110
- Amphetamines
Risk Factors, 79-7160
- Appendectomy
Risk Factors, 79-7160
- Carcinogen, Chemical
Occupational Hazard, 79-7154
- Carcinoma, Epidermoid
Immunologic Deficiency Syndromes
79-7088
- Child
Epidemiology, Iraq, 79-7161
- Epidemiology
Saudi Arabia, 79-7146
- Ethnic Groups
Epidemiology, Los Angeles, 79-7160
- Nodular Sclerosis, 79-7160
- Horizontal Transmission
Epidemiology, 79-7162
- Immunologic Deficiency Syndromes
Radiation, Drug Therapy, 79-7088
- Lymph Nodes
Diagnosis and Classification, 79-7110
- Mycosis Fungoides
Case Report, 79-7111
- Neoplasm Metastasis
Subtype, 79-7161
- Neoplasms, Multiple Primary
Adenocarcinoma, 79-7088
- Carcinoma, Epidermoid, 79-7088

Hodgkin's Disease (cont'd)

- Occupational Hazard
Epidemiology, 79-7176
- Epidemiology, Sweden, 79-7154
- Solvents
Air Pollution, 79-7165
- Thyroid Neoplasms
Radiotherapy, 79-7166
- Wounds and Injuries
Axilla, 79-7153

Homocysteine, S-Adenosyl-

- Virus, Rous Sarcoma
Protein Arginine Methyltransferase
79-6939

Hormones

- Leydig Cell Tumor
Age Factors, Rat, 79-7137

Hyaluronic Acid

- Mammary Neoplasms, Experimental
Carcinoma, Ductal, 79-7199

Hycanthone Methanesulfonate

- Hepatoma
Carcinogenic Potential, Mouse
79-6779
- Liver Neoplasms
Carcinogenic Potential, Mouse
79-6779
- Sarcoma, 79-6779

Hydatidiform Mole

- Epidemiology
Greenland, 79-7147

Hydrazine, 1,2-Dimethyl-

- Bile
Ames Test, 79-6768
- Mutagenic Metabolite, 79-6768
- Colonic Neoplasms
Cholecystectomy, 79-6631
- Intestinal Neoplasms
Adenocarcinoma, 79-6674
- Adenoma, 79-6673, 79-6674
- Barbituric Acid, 5-Ethyl-5-phenyl-,
Sodium Salt, 79-6675
- p*-Cresol, 2,6-Di-*tert*-butyl-, 79-6674
- Lung Neoplasms
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6674

1,2-Hydrazinedicarbothioamide

- Hepatoma
Dose-Response Study, 79-6717

Hydrazoic Acid

- Tridascantia paludosa*
Mutagenic Activity, 79-6899

Hydroxylamine, N-4-Biphenyl-

- Glucuronates
Microsomal, Urinary Conjugates
79-6767
- Uridine Diphosphate Sugars
Metabolism, 79-6767

Hydroxylamine, N-Fluorene-2-yl-

- DNA
Nucleic Acid Denaturation, 79-6691
- Guanosine, 2'-Deoxy-
Endonucleases, 79-6691

Hyperplasia

- Acetamide, N-Fluorene-2-yl-
Barbituric Acid, 5-Ethyl-5-phenyl-
79-6687
- 5,6-Benzoflavone, 79-6687
- Cholanthrene, 3-Methyl-, 79-6687
- Kanechlor 500, 79-6687
- Adrenal Gland Neoplasms
Pentadecane, 2,6,10,14-Tetramethyl-
79-6672
- Petroleum, 79-6672
- Aroclor 1254
Epidermis, Mouse, 79-6813
- Bladder Neoplasms
Precancerous Conditions, Rat, 79-6733
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Epidermis, Mouse, 79-6813

Hyperplasia (cont'd)

- Epoxide Hydratases
- Endoplasmic Reticulum, 79-6684
- Estradiol
- Retinol Acetate, 79-6853
- Hepatoma
- Acetamide, *N*-Fluoren-2-yl-, 79-7123
- Diethylamine, *N*-Nitroso-, 79-7123
- Kepone, 79-6782
- Kidney Neoplasms
- Pentadecane, 2,6,10,14-Tetramethyl-, 79-6672
- Petroleum, 79-6672
- p*-Phenylenediamine, 2-Chloro-, Sulfate 79-6759

Liver

- Bile Canaliculi, 79-7123
- Liver Neoplasms
- Acetamide, *N*-Fluoren-2-yl-, 79-6684
- 79-6688
- Contraceptives, Oral, 79-6855
- Epoxide Hydratases, 79-6684
- Skin Neoplasms
- Ornithine Decarboxylase, 79-6800
- Vaginal Neoplasms
- Estradiol, 79-6853

Hypersensitivity, Delayed

- Melanoma
- Antigens, Neoplasm, 79-7087

Hyperthermia

- Abnormalities
- Hamster, 79-6900
- Retinol
- Teratogenic Interactions, 79-6900

Hypoxanthine Phosphoribosyltransferase

- Chromosomes
- Gene Transfer, 79-7186

IA-4 *N*-Oxide

- Liver Neoplasms
- Carcinogenic Potential, Mouse 79-6779

ICR 170

- Thioguanine Resistance
- Mutagenic Activity, 79-6723

ICR 220

- Thioguanine Resistance
- Mutagenic Activity, 79-6723

ICR 342

- Thioguanine Resistance
- Mutagenic Activity, 79-6723

IgG

- Immune Complex Disease
- Complement Fixation, 79-7085
- Interferon
- Immunosuppression, 79-6988
- Melanoma
- Antigen-Antibody Complex, 79-7085
- Plasmacytoma
- Polyribosomes, 79-7192
- RNA, Messenger, 79-7192
- Virus, Adeno 12
- Phosphoproteins, 79-7047
- Virus, Moloney Murine Sarcoma
- Immune Serums, 79-7072

IgM

- Breast Neoplasms
- Immune Response, 79-7149
- Plasma Levels, 79-7149
- Leukemia, Myelocytic
- B-Lymphocytes, 79-7107
- Virus, Epstein-Barr
- Cells, Cultured, 79-7015
- Virus, Moloney Murine Sarcoma
- Immune Serums, 79-7072

Imidazole, 1,2-Dimethyl-5-nitro-

- Chromosome Aberrations
- Micronucleus Test, 79-6735

1*H*-Imidazole-2-methanol, 1-Methyl-5-

- nitro-, Carbamate (Ester)
- Chromosome Aberrations
- Micronucleus Test, 79-6735

2-Imidazolidinethione, *N*-Nitroso-

- Lung Neoplasms
- Adenocarcinoma, 79-6736

2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-

- Kidney Neoplasms
- Adenocarcinoma, 79-6868
- Adenoma, 79-6868
- Mesenchymoma, 79-6868
- Nephrosclerosis
- Precancerous Conditions, 79-6868

Immune Serums

- Aflatoxin G1
- Antibody Specificity, 79-6789
- Aflatoxin M1
- Antibodies, 79-6789
- Antibody Specificity, 79-6789
- Intestinal Neoplasms
- Adenocarcinoma, 79-6916
- Nephroblastoma
- Antigens, Neoplasm, 79-7096
- Radiation, Ionizing
- Blocking Factors, 79-6916
- Virus, Adeno 12
- Antigens, Neoplasm, 79-7047
- Virus, Feline Leukemia
- Inactivating Factor, 79-7001
- Virus, Friend Murine Leukemia
- Antigen-Antibody Reactions, 79-6977
- Virus, Moloney Murine Sarcoma
- IgG, 79-7072
- IgM, 79-7072
- Virus, Murine Leukemia
- Inactivating Factor, 79-7001
- Lipoproteins, 79-7001

Immunity, Cellular

- Intestinal Neoplasms
- Radiation, Ionizing, 79-6916
- Killer Cells
- Spleen, Mouse, 79-7075
- Melanoma
- Transplantation, Homologous, 79-7089
- Neoplasms, Experimental
- Age Factors, Hamster, 79-7064
- Hybrid Cells, 79-7066
- Virus, Murine Sarcoma, 79-7065
- Radiation, Ionizing
- Hamster, 79-6915
- Skin Neoplasms
- Ultraviolet Rays, 79-6887
- Virus, Friend Murine Leukemia
- T-Lymphocytes, 79-6980
- Virus, Gross Murine Leukemia
- T-Lymphocytes, 79-6980
- Virus, Rauscher Murine Leukemia
- Antigenic Determinants, 79-6991
- T-Lymphocytes, 79-6980
- Virus, Rous Sarcoma
- Antigens, Neoplasm, 79-6952

Immunity, Passive

- Virus, Marek's Disease Herpes
- Killer Cells, 79-6955
- Virus, Rous Sarcoma
- Tumor Latency, 79-6942

Immunization

- Mammary Neoplasms, Experimental
- Hybrid Cells, 79-6967

Immunoblastic Lymphadenopathy

- Immunologic Deficiency Syndromes
- B-Lymphocytes, 79-7112
- T-Lymphocytes, 79-7112
- B-Lymphocytes
- Case Report, Child, 79-7112
- Thymus Gland
- Transplantation, 79-7112

Immunologic Deficiency Syndromes

- Adenocarcinoma
- Hodgkin's Disease, 79-7088

Immunologic Deficiency Syndromes (cont'd)

- Carcinoma, Epidermoid
- Hodgkin's Disease, 79-7088
- Immunoblastic Lymphadenopathy
- B-Lymphocytes, 79-7112
- T-Lymphocytes, 79-7112
- Melanoma
- Nevus, 79-7084

Immunosuppression

- Interferon
- IgG, 79-6988
- Neoplasms, Experimental
- Macrophages, 79-7065
- Sarcoma
- Virus, Murine Sarcoma, 79-6960
- Virus, Marek's Disease Herpes
- Virus, Avian Reticuloendotheliosis 79-7068
- Virus, Murine Sarcoma
- Leukocyte Culture Test, Mixed 79-6960
- Virus, SV40
- Plasmodium berghei yoelii*, 79-7041

Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-

- 5-methoxy-2-methyl-
- 12-*O*-Tetradecanoylphorbol-13-acetate
- Prostaglandins E, 79-6795

Insulin

- Breast Neoplasms
- Growth, 79-7200
- Cell Transformation, Neoplastic
- Cell Cycle Kinetics, 79-7187

Interferon

- Cell Transformation, Neoplastic
- Antiviral Effects, 79-6983
- Fibroblasts, 79-6983

IgG

- Immunosuppression, 79-6988
- Virus, Kirsten Murine Leukemia
- Cell Transformation, Neoplastic 79-6983
- Virus, Moloney Murine Sarcoma
- Anti-Antibodies, 79-6988
- Virus, Murine Sarcoma
- Cell Transformation, Neoplastic 79-6983

Intestinal Neoplasms

- Adenocarcinoma
- Histological Study, Rat, 79-6673
- Hydrazine, 1,2-Dimethyl-, 79-6674
- Immune Serums, 79-6916
- Methane, Azoxy-, 79-6860
- Precancerous Conditions, 79-6673
- Radiation, Ionizing, 79-6916, 79-6917
- Adenoma
- Hydrazine, 1,2-Dimethyl-, 79-6673
- 79-6674
- Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt
- Co-carcinogenic Effect, 79-6675
- Carcinoma, Mucinous
- Radiation, Ionizing, 79-6917
- Cecal Neoplasms
- Radiotherapy, 79-6917
- Gynecologic Neoplasms
- Radiotherapy, 79-6917
- Hydrazine, 1,2-Dimethyl-
- Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt, 79-6675
- p*-Cresol, 2,6-Di-*tert*-butyl-, 79-6674
- Methane, Azoxy-
- Dietary Fats, 79-6860
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
- Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt, 79-6675
- Radiation, Ionizing
- Immunity, Cellular, 79-6916

Iodoform

- see Methane, Triiodo-

Iron Oxide

- Benzo(a)pyrene
 - Transport, Microsomes, 79-6831
- Lung Neoplasms
 - Polonium, 79-6922
- Tracheal Neoplasms
 - Cholanthrene, 3-Methyl-, 79-6824

Islet Cell Tumor

- Hippel-Lindau Disease
 - Case Report, 79-7124
- Pancreatic Neoplasms
 - Guthion, 79-6777

Isonicotinic Acid Hydrazide

- Carcinogenic Metabolite
 - Liver, Review, 79-6616

Isoproterenol

- Aryl Hydrocarbon Hydroxylases
 - Lymphocytes, 79-6819
- Mezerein
 - Adenosine Cyclic 3',5' Monophosphate, 79-6800
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Adenosine Cyclic 3',5' Monophosphate, 79-6800

Jaw Neoplasms

- Ameloblastoma
 - Urea, Ethyl Nitroso-, 79-6715

Kanechlor 500

- Hyperplasia
 - Acetamide, *N*-Fluoren-2-yl-, 79-6687

Karyotyping

- Brain Neoplasms
 - Meningioma, 79-7099
- Kidney Neoplasms
 - Leukocytes, 79-7127
- Leukemia, Myelocytic
 - Eosinophilia, 79-7108
- Spinal Cord Neoplasms
 - Meningioma, 79-7099

Kepone

- Hepatoma
 - Carcinogenic Activity, Rat, 79-6782
- Hyperplasia, 79-6782

Keratin

- Benzo(a)pyrene
 - Cell Transformation, Neoplastic

79-6833

Keratosis

- Carcinoma, Epidermoid
 - Heat, 79-6911

Kidney Diseases

- Acetic Acid, (2,4,5-Trichlorophenoxy)-
 - Toxicity, Rat, 79-6677

Kidney Neoplasms

- Adenocarcinoma
 - Acetanilide, 4'-(*p*-Fluorophenyl)-
 - 79-6689
 - Acetic Acid, Lead Salt, 79-6689
 - Amidophosphoribosyltransferase
 - 79-7196
 - Cholesterol, 79-7197
 - Genetics, 79-7127
 - 2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-, 79-6868
 - Sertoli Cell Tumor, 79-6792
 - Virus, Herpes Lucke, 79-7169
- Adenoma
 - Dimethylamine, *N*-Nitroso-, 79-6863
 - 2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-, 79-6868
- Benzene, 4-Allyl-1,2-(methylenedioxy)-
 - Transplacental Carcinogenesis
- 79-6748
- Carcinoma
 - Dimethylamine, *N*-Nitroso-, 79-6863
 - Virus, DNA Tumor, 79-7051
- Chromosome Aberrations
 - Chromosomes, Human, 4-5, 79-7127

Kidney Neoplasms (cont'd)

- Chromosomes, Human, 6-12, 79-7127
- Dimethylamine, *N*-Nitroso-
 - Age Factors, Rat, 79-6863
- Fibroma
 - Dimethylamine, *N*-Nitroso-, 79-6863
- Hyperplasia
 - Pentadecane, 2,6,10,14-Tetramethyl-
 - 79-6672
 - Petroleum, 79-6672
 - p*-Phenylenediamine, 2-Chloro-, Sulfate
 - 79-6759
- Karyotyping
 - Leukocytes, 79-7127
- Mesenchymoma
 - Dimethylamine, *N*-Nitroso-, 79-6863
 - 2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-, 79-6868
- Nephroblastoma
 - Urea, Ethyl Nitroso-, 79-6715
- p*-Phenylenediamine, 2-Chloro-, Sulfate
 - Carcinogenic Potential, 79-6759
- Teratoid Tumor
 - Urea, Ethyl Nitroso-, 79-6715

Kidney Tubules

- Benzenediazosulfonic Acid, *p*-(Dimethylamino)-, Sodium Salt
 - Necrosis, 79-6656

L Cells

- Actinomycin D
 - Polyribosomes, 79-7192
- Benz(a)anthracene, 7-Bromo-methyl-12-methyl-
 - DNA Repair, 79-6805
- Benz(a)anthracene, 7-Bromomethyl-
 - DNA Repair, 79-6805
- Hybrid Cells
 - Histocompatibility Antigens, 79-7092
 - Immunologic Techniques, 79-7066
- Mammary Neoplasms, Experimental
 - Hybrid Cells, 79-6967, 79-7092
- Proteins
 - Temperature, 79-7192
- Tannic Acid
 - DNA Replication, 79-6786

Lactate Dehydrogenase

- 4,4'-Bipyridinium, 1,1'-Dimethyl-, Dichloride
 - Enzymatic Activity, 79-6698
- Carbamic Acid, Ethyl Ester
 - Lung, Mouse, 79-6698
- p*-Cresol, 2,6-Di-*tert*-butyl-
 - Enzymatic Activity, 79-6698
- Dimethylamine, *N*-Nitroso-
 - Lung, Mouse, 79-6698
- Lung Neoplasms
 - Adenoma, 79-6698
- Nephroblastoma
 - Chromosomes, Human, 6-12, 79-7126

Laryngeal Neoplasms

- Carcinoma, Epidermoid
 - Radiation, Ionizing, 79-7140
- Diethylamine, *N*-Nitroso-
 - Transplacental Carcinogenesis
- 79-6725
- Ethyl Alcohol
 - Epidemiology, 79-7181
- Glucuronidase
 - Neutrophils, 79-7090
- Precancerous Conditions, 79-7090
- Papilloma
 - Diethylamine, *N*-Nitroso-, 79-6725
- Polyps
 - Diethylamine, *N*-Nitroso-, 79-6725
- Radiation, Ionizing
 - Dental X-Rays, 79-7181
- Epidemiology, 79-7140
- Smoking
 - Animal Model, Hamster, 79-6822
- Epidemiology, 79-7181
- Precancerous Conditions, 79-6845
- Retinol Palmitate, 79-6845
- Solvents
 - Air Pollution, 79-7165

Lasiocarpine

- Ames Test
 - Pyrrolizidine Alkaloids, 79-6776
- S9 Fraction, 79-6776

Lead

- Multiple Myeloma
 - Occupational Hazard, 79-7176

Lead, Bis(dimethyldithiocarbamate)-

- Dose-Response Study
 - Carcinogenic Potential, 79-6648

Lens Diseases

- Coloboma
 - Chromosome Aberrations, 79-7102

Leukemia

- Age Factors
 - Cat, 79-7163
- Alanine, 3-(*p*-(Bis(2-chloroethyl)amino)phenyl)-
 - Epidemiology, 79-7155
- Anemia, Sideroblastic
 - Epidemiology, 79-7164
- Precancerous Conditions, 79-7164
- Antigens, Neoplasm
 - Transplantation Immunology, 79-6878
- Benzene
 - Occupational Hazard, 79-7176
- 1,1'-Biphenyl, 4,4'-Diisocyanato-3,3'-dimethoxy-
 - Carcinogenic Potential, 79-6769
- Child
 - Genetics, Review, 79-6637
- Cyanamide, Calcium Salt
 - Carcinogenic Potential, 79-6647
- Dibenzo-*p*-dioxin, 2,7-Dichloro-
 - Carcinogenic Potential, 79-6774
- Epidemiology
 - Printers, 79-7176
- Histocompatibility Antigens
 - Transplantation Immunology, 79-6878
- Horizontal Transmission
 - Epidemiology, 79-7162
- T-Lymphocytes
 - Immunosuppression, 79-7070
- Multiple Myeloma
 - Drug Therapy, 79-7155
- Phenol, 2,4,6-Trichloro-
 - Dose-Response Study, 79-6747
- Prednisone
 - Epidemiology, 79-7155
- Scleroderma
 - Lymphoma, 79-7158
- Solvents
 - Air Pollution, 79-7165
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-
 - Carcinogenic Potential, 79-6750
- Ultraviolet Rays
 - Immune Response, Mouse, 79-6878
- Lymphocyte Culture Test, Mixed
 - 79-7070
- Urea, 1-(*p*-Acetylphenyl)sulfonyl-3-cyclohexyl-
 - Dose-Response Study, 79-6720
- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 - Epidemiology, 79-7155
- Virus, AKR Murine Leukemia
 - Genes, Viral, 79-6989
- Virus, Feline Leukemia
 - Seroepidemiology, 79-7163
- Virus, Friend Murine Leukemia
 - Benzo(a)pyrene, 79-7070
- T-Lymphocytes, 79-6980
- Precancerous Conditions, 79-6976
- Virus, Gross Murine Leukemia
 - T-Lymphocytes, 79-6980
- Virus, Moloney Murine Leukemia
 - Genes, Viral, 79-6989
- Virus, Rauscher Murine Leukemia
 - T-Lymphocytes, 79-6980

Leukemia L1210

- Radiation, Ionizing
 - DNA Repair, 79-6904

Leukemia, Lymphoblastic
 Dwarfism
 Case Report, 79-7109
 Telangiectasis
 Chromosome Abnormalities, 79-7109
 Virus, Baboon C-Type RNA Tumor
 Hybrid Cells, 79-7002

Leukemia, Lymphocytic
 2-Imidazolidinethione, *N*-Nitroso-
 Dose-Response Study, 79-6736

Leukemia, Myeloblastic
 Antibodies
 Rosette Formation, 79-7074
 Chromosome Aberrations
 Chromosomes, Human, 4-5, 79-7106
 Epidemiology
 England, 79-7152
 Granulocytes
 Cell Differentiation, 79-7193
 Leukemia, Myelocytic
 Case Report, 79-7113
 Leukocytes
 Receptors, Fc, 79-7074
 Lymphosarcoma
 Epidemiology, 79-7105
 Macrophages
 Cell Differentiation, 79-7193
 Neoplasms, Multiple Primary
 Drug Therapy, 79-7105
 Radiotherapy, 79-7105
 Sarcoma, Reticulum Cell
 Epidemiology, 79-7105
 Virus, Baboon C-Type RNA Tumor
 Hybrid Cells, 79-7002

Leukemia, Myelocytic
 Antibodies
 Rosette Formation, 79-7074
 Bone Marrow
 Cell Differentiation, 79-6794
 Cell Differentiation
 Muramidase, 79-6796
 Phagocytosis, 79-6796
 Rosette Formation, 79-6796
 Chromosomes, Human, 21-22
 Blast Crisis, 79-7107
 Eosinophilia
 Case Report, 79-7108
 Karyotyping, 79-7108
 Epidemiology
 England, 79-7152
 Granulocytes
 Cell Differentiation, 79-7073
 Leukemia, Myeloblastic
 Case Report, 79-7113
 Leukocytes
 Receptors, Fc, 79-7074
 B-Lymphocytes
 IgM, 79-7107
 Mesenchymoma
 Transplantation, Heterologous
 79-7118
 Phorbol Esters
 Cell Differentiation, 79-6796
 Teleocidin B, Dihydro
 Cell Adhesion, 79-6844
 12-*O*-Tetradecanoylphorbol-13-acetate
 Cell Differentiation, 79-6794, 79-6796
 Phagocytosis, 79-6794
 Transplantation Immunology
 Killer Cells, 79-7075

Leukemia, Radiation-Induced
 Radiation, Ionizing
 Theoretical Model, Mouse, 79-6903
 Viral Proteins, 79-6903
 Viral Proteins
 Mutation, Mouse, 79-6903

Leukocytes
 Kidney Neoplasms
 Karyotyping, 79-7127
 Leukemia, Myeloblastic
 Receptors, Fc, 79-7074
 Leukemia, Myelocytic
 Receptors, Fc, 79-7074

Leydig Cell Tumor
 Hormones
 Age Factors, Rat, 79-7137
 Testicular Neoplasms
 Estradiol, 79-7137
 Fenthion, 79-6654
 Prolactin, 79-7137

LH
 Mammary Neoplasms, Experimental
 Progesterone, 79-6857
 R2323, 79-6857

Light
 Chromosome Aberrations
 Cells, Cultured, 79-6894
 Eye Neoplasms
 Transplantation, Homologous, 79-6894
 Oxygen
 Cell Transformation, Neoplastic
 79-6894

Lip Neoplasms
 Carcinoma, Epidermoid
 Lupus Erythematosus, Discoid
 79-7103

Lipopolysaccharides
 12-*O*-Tetradecanoylphorbol-13-acetate
 Cell Differentiation, 79-6796

Lipoproteins
 Virus, Murine Leukemia
 Immune Serums, 79-7001

Liver Neoplasms
 Acetamide, *N*-Fluoren-2-yl-
 2,4-Oxazolidinedione, 3-(3,5-
 Dichlorophenyl)-5,5-dimethyl-
 79-6687
 Precancerous Conditions, 79-6687
 Selenium, 79-6685
 Serine, Diazoacetate (Ester), 79-6683
 Adenoma
 Contraceptives, Oral, 79-6855
 Ethane, 1,1-Dichloro-2,2-bis(*p*-
 ethylphenyl)-, 79-6665
 Phenol, 2,4,6-Trichloro-, 79-6747
 Aflatoxin B1
 Amaranth, 79-6791
Bacterioides multiaacidus
 Mouse, 79-6643
 Chrysene
 Carcinogenic Activity, Mouse, 79-6861
 Contraceptives, Oral
 Histological Study, 79-6855
p-Cresol, 2,6-Di-*tert*-butyl-
 Carcinogenic Potential, 79-6753
Escherichia coli
 Mouse, 79-6643
 Hemangioendothelioma
 Thorium Dioxide, 79-6770
 Hycanthone Methanesulfonate
 Carcinogenic Potential, Mouse
 79-6779
 Hyperplasia
 Acetamide, *N*-Fluoren-2-yl-, 79-6684
 79-6688
 Contraceptives, Oral, 79-6855
 Epoxide Hydratases, 79-6684
 1A-4 *N*-Oxide
 Carcinogenic Potential, Mouse
 79-6779
 Precancerous Conditions
 Iron Accumulation, 79-6688
 Radiation, Ionizing
 Hamster, 79-6915
 Virus-Like Particles, 79-6915
 Sarcoma
 Hycanthone Methanesulfonate
 79-6779
 Virus, SV40, 79-7041
 Serine, Diazoacetate (Ester)
 Choline, 79-6683
 Precancerous Conditions, 79-6683
Streptococcus faecalis
 Mouse, 79-6643

Liver Regeneration
 Virus, Moloney Murine Leukemia
 RNA, Viral, 79-6986
 Virus, Murine Leukemia
 RNA, Viral, 79-6986

Lung Neoplasms
 Adenocarcinoma
 2-Imidazolidinethione, *N*-Nitroso-
 79-6736
 Neoplasm Metastasis, 79-6728
 Polonium, 79-6922
 Adenocarcinoma, Papillary
 Virus, SV40, 79-7041
 Adenoma
 Carbamic Acid, Ethyl Ester, 79-6699
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6753
 Diphenylamine, *N*-Nitroso-, 79-6730
 Lactate Dehydrogenase, 79-6698
 1,5-Naphthalenediamine, 79-6772
 Phthalic Anhydride, 79-6762
 Terephthalic Acid, Dimethyl Ester
 79-6749
p-Toluamide, *N*-Isopropyl- α -(2-
 methylhydrazino)-, 79-6750
 Urea, Ethyl Nitroso-, 79-6714
 Virus, SV40, 79-7041
 Alpha Particles
 Microspheres, 79-6921
 Antigens, Neoplasm
 Fetal Globulins, 79-7091
 Asbestos
 Histocompatibility Antigens, 79-6650
 Smoking, 79-6650
 Benz(a)anthracene, 7,12-Dimethyl-
 Transplacental Carcinogenesis
 79-6618
 Benzo(a)pyrene
 Virus, Influenza, 79-6633
 Carbamic Acid, Diethylidithio-, 2-
 Chloroallyl Ester
 Carcinogenic Potential, 79-6702
 Carbamic Acid, Ethyl Ester
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6699
 Virus, Influenza, 79-6633
 Carbon Tetrabromide
 Carcinogenic Activity, Mouse, 79-6666
 Carcinoma
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6753
 Carcinoma, Epidermoid
 Antigens, Neoplasm, 79-7091
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 79-6773
 Epidemiology, 79-7138
 Polonium, 79-6922
 Radioisotopes, 79-6896
 Carcinoma, Oat Cell
 Epidemiology, 79-7138
 Ultrastructural Study, 79-7119
p-Cresol, 2,6-Di-*tert*-butyl-
 Carcinogenic Potential, 79-6753
 Diethylamine, *N*-Nitroso-
 Virus, Influenza, 79-6633
 Ethnic Groups
 Epidemiology, Louisiana, 79-7179
 Hydrazine, 1,2-Dimethyl-
p-Cresol, 2,6-Di-*tert*-butyl-, 79-6674
 Neoplasms, Multiple Primary
 Chrysene, 1,2-Dihydro-1,2-dihydroxy-
 79-6861
 Chrysene, 3,4-Dihydro-3,4-dihydroxy
 79-6861
 Chrysene, 1,2-Dihydroxy-3,4-oxy-
 1,2,3,4-tetrahydro-, 79-6861
 Occupational Hazard
 Epidemiology, Louisiana, 79-7179
 Phenanthrene, 1,2-Dihydro-3,4-oxy-
 1,2,3,4-tetrahydro-
 Carcinogenic Activity, Mouse, 79-6861
 Phthalic Anhydride
 Carcinogenic Potential, 79-6762
 Plutonium Dioxide
 Inhalation Study, Hamster, 79-6921
 Pneumonitis
 Co-carcinogenic Effect, Rat, 79-6896
 Polonium
 Iron Oxide, 79-6922

Lung Neoplasms (cont'd)

- Propane, 1,2-Dibromo-3-chloro-Carcinogenic Activity, Mouse, 79-6666
- Propene, 1,3-Dichloro-Carcinogenic Activity, Mouse, 79-6666
- Rhodium
 - Radioisotopes, 79-6896
- Ruthenium
 - Radioisotopes, 79-6896
- Smoking
 - Sex Factors, 79-7138
 - Virus, Influenza, 79-6633
- Thyroiditis, Lymphomatous
 - Epidemiology, Japan, 79-7139
- Urea, Ethyl Nitroso-Amniotic Fluid Injection, 79-6714
- Transplacental Carcinogenesis, Review 79-6608
- Virus, Influenza
 - Co-carcinogenic Effect, Review 79-6633
- Wounds and Injuries
 - Neoplasm Metastasis, 79-6657
- Zirconium Dioxide
 - Inhalation Study, Hamster, 79-6921

Lupus Erythematosus, Discoid

- Lip Neoplasms
 - Carcinoma, Epidermoid, 79-7103

Lymphocyte Transformation

- Virus, Rous Sarcoma
 - Plant Agglutinins, 79-6952

Lymphocytes

- Azathioprine
 - Chromosome Aberrations, 79-6781
- Cadmium Chloride
 - Immune Response, 79-6645
 - Metalloproteins, 79-6645
- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 - Azaguanine Resistance, 79-6700
- Estradiol, 17-Ethynyl-Chromatids, 79-6856
- Ethylene, Chloro-
 - Chromosome Aberrations, 79-6662
- Melanoma
 - Antigens, Neoplasm, 79-7087
- Norgestrel
 - Chromatids, 79-6856
- 2-Oxetanone
 - Azaguanine Resistance, 79-6700
- Plasmacytoma
 - A-Type Particles, 79-7055
- Polycyclic Hydrocarbons
 - Aryl Hydrocarbon Hydroxylases 79-6819
- Retinoblastoma
 - Chromosome Aberrations, 79-7101
- Tannic Acid
 - DNA Replication, 79-6786
- Ultrasonics
 - Chromatids, 79-6925
- Ultraviolet Rays
 - Suppressor Cells, 79-6879

B-Lymphocytes

- Immunoblastic Lymphadenopathy
 - Case Report, Child, 79-7112
 - Immunologic Deficiency Syndromes 79-7112
- Leukemia, Myelocytic
 - IgM, 79-7107
- Lymphosarcoma
 - Immune Response, 79-7078
- Sarcoma Kaposi's
 - Immune Response, 79-7114
- Sarcoma, Reticulum Cell
 - Case Report, Child, 79-7112
- Virus, Epstein-Barr
 - Deoxyribonuclease, 79-7014
- Virus, Guinea Pig Herpes
 - Virus Replication, 79-6995

T-Lymphocytes

- Graft vs Host Reaction
 - Age Factors, Hamster, 79-7064

T-Lymphocytes (cont'd)

- Immunoblastic Lymphadenopathy
 - Immunologic Deficiency Syndromes 79-7112
- Leukemia
 - Immunosuppression, 79-7070
 - Virus, Friend Murine Leukemia 79-6980
 - Virus, Gross Murine Leukemia 79-6980
 - Virus, Rauscher Murine Leukemia 79-6980
- Myasthenia Gravis
 - Lymphocyte Depletion, 79-7076
- Sarcoma
 - Cholanthrene, 3-Methyl-, 79-7082
 - Growth, 79-7082
 - Suppressor Cells, 79-7082
 - Virus, Moloney Murine Leukemia 79-7082
- Virus, Adeno 2
 - Antilymphocyte Serum, 79-7042
- Virus, AKR Murine Leukemia
 - Cell Differentiation, 79-7069
 - Immune Response, 79-7069
- Virus, Feline Leukemia
 - Virus Replication, 79-7000
- Virus, Friend Murine Leukemia
 - Immunity, Cellular, 79-6980
- Virus, Gross Murine Leukemia
 - Antigens, Viral, 79-6981
 - Histocompatibility Antigens, 79-6980
 - Immunity, Cellular, 79-6980
- Virus, Guinea Pig Herpes
 - Virus Replication, 79-6995
- Virus, Murine Sarcoma
 - Antilymphocyte Serum, 79-6960
 - Suppressor Cells, 79-6960
- Virus, Rauscher Murine Leukemia
 - Histocompatibility Antigens, 79-6991
 - Immunity, Cellular, 79-6980
- Virus, Rous Sarcoma
 - Antilymphocyte Serum, 79-6942

Lymphoma (General and Unspecified)

- Age Factors
 - Cat, 79-7163
- Antigens, Viral
 - Immunologic Techniques, 79-7061
- Benzo(a)pyrene
 - Lymphocyte Culture Test, Mixed 79-7070
- 1,1'-Biphenyl, 4,4'-Diisocyanato-3,3'-dimethoxy-
 - Carcinogenic Potential, 79-6769
- 2-Butanone
 - Air Pollution, 79-7165
- Cyanamide, Calcium Salt
 - Carcinogenic Potential, 79-6647
- Dibenzo(b,def)chrysene-7,12-dione
 - Dose-Response Study, 79-6820
- Dibenzo-*p*-dioxin, 2,7-Dichloro-
 - Carcinogenic Potential, 79-6774
- Epidemiology
 - Saudi Arabia, 79-7146
- Horizontal Transmission
 - Epidemiology, 79-7162
- Hybrid Cells
 - Histocompatibility Antigens, 79-7071
 - Transplantation Immunology, 79-7071
- Kidney Transplantation
 - Epidemiology, 79-7142
- Leukemia
 - Scleroderma, 79-7158
- Macrophages
 - Neoplasm Metastasis, 79-7077
- Myasthenia Gravis
 - Case Report, 79-7076
 - Radiotherapy, 79-7076
- 2-Pentanone, 4-Methyl-
 - Air Pollution, 79-7165
- Phenol, 2,4,6-Trichloro-
 - Dose-Response Study, 79-6747
- Phthalic Anhydride
 - Carcinogenic Potential, 79-6762
- Radiation, Ionizing
 - Neoplasm Metastasis, 79-7077

Lymphoma (General and Unspecified) (cont'd)

- Receptors, Fc
 - Immune Response, 79-7077
- Scleroderma
 - Epidemiology, 79-7158
- Terephthalic Acid, Dimethyl Ester
 - Carcinogenic Potential, 79-6749
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-
 - Carcinogenic Potential, 79-6750
- Transplantation Immunology
 - Killer Cells, 79-7075
- Ultraviolet Rays
 - Mutagenic, Toxic Effects, 79-6880
- Urea, 1-((*p*-Acetylphenyl)sulfonyl)-3-cyclohexyl-
 - Dose-Response Study, 79-6720
- Virus, Feline Leukemia
 - Seroepidemiology, 79-7163
- Virus, Herpes Simplex 1
 - Antigens, Viral, 79-7007
- Virus, Herpes Simplex 2
 - Antigens, Viral, 79-7007
- Virus, Moloney Murine Leukemia
 - Antigens, Neoplasm, 79-6987
 - Antigens, Viral, 79-6987
- Mammary Neoplasms, Experimental 79-7071
- Virus, Murine Mammary Tumor
 - Peptides, 79-6965
- Virus-Like Particles, 79-6965
- Virus, Newcastle Disease
 - Cell Membrane, 79-7061
- Virus, Radiation Leukemia
 - Virus, Helper, 79-7056
- Virus, Sendai
 - Cell Membrane, 79-7061

Lymphosarcoma

- 2-Imidazolidinethione, *N*-Nitroso-
 - Dose-Response Study, 79-6736
- Leukemia, Myeloblastic
 - Epidemiology, 79-7105
- B-Lymphocytes
 - Immune Response, 79-7078
- Urea, Ethyl Nitroso-
 - Carcinogenic Activity, Mouse, 79-6712
- Urea, 1-(2-Hydroxyethyl)-1-nitroso-
 - Carcinogenic Activity, Mouse, 79-6712
- Virus, Feline Leukemia
 - Urea, Methyl Nitroso-, 79-6999

Macrophages

- Arthritis, Adjuvant
 - Mycobacterium butyricum*, 79-7081
- Benzo(a)pyrene
 - Sister Chromatid Exchange, 79-6834
- Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
 - Sister Chromatid Exchange, 79-6834
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - Sister Chromatid Exchange, 79-6834
- Granulocytes
 - Contact Inhibition, 79-7193
- Hepatoma
 - Chemotaxis Inhibitor, 79-7095
 - Growth, 79-7081
 - Virus, Lactate Dehydrogenase 79-7095
- Leukemia, Myeloblastic
 - Cell Differentiation, 79-7193
- Lymphoma
 - Neoplasm Metastasis, 79-7077
- Mycobacterium butyricum*
 - Antitumor Activity, 79-7081
- Neoplasms, Experimental
 - Immunosuppression, 79-7065
- Prostaglandins E
 - Colony Stimulating Factor, 79-7073
- Sarcoma, Yoshida
 - Growth, 79-7081

Mammary Neoplasms, Experimental

- Adenocarcinoma
 - Benz(a)anthracene, 7,12-Dimethyl-79-6667, 79-6817

Mammary Neoplasms, Experimental (cont'd)
 Carbamic Acid, Diethylthio-, 2-Chloroallyl Ester, 79-6702
 Methanesulfonic Acid, Ethyl Ester 79-6649
 Sialyltransferase, 79-6817
 4,4'-Stilbenediol, α,α' -Diethyl- 79-6847
p-Toluidine, *N*-Isopropyl- α -(2-methylhydrazino)-, 79-6750
Adenofibroma
 Benz(a)anthracene, 7,12-Dimethyl- 79-6667
 Carcinogenic Potential, 79-6752
 Radiation, Ionizing, 79-6847
 4,4'-Stilbenediol, α,α' -Diethyl- 79-6847
 Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)- 79-6713
Adenoma
 Mucopolysaccharides, 79-7199
 Benz(a)anthracene, 7,12-Dimethyl-Ethylene, 1-Bromo-2-*p*-(ethylphenyl)-1,2-diphenyl-, 79-6667
 Gonadotropins, 79-6811
 Hormone Imbalance, 79-6850
 Precancerous Conditions, 79-6818 79-6963
 Progesterone, 79-6857
 Prolactin, 79-6818
 R2323, 79-6857
 Somatotropin, 79-6811
 Thyrotropin, 79-6811
 Thyrotropin Releasing Hormone 79-6811
 Transplacental Carcinogenesis 79-6618
 Virus, Murine Mammary Tumor 79-6969
Carcinoma
 Mucopolysaccharides, 79-7199
Carcinoma, Ductal
 Chondroitin, 79-7199
 Hyaluronic Acid, 79-7199
Cholanthrene, 3-Methyl-
 Animal Model, Hamster, 79-6822
 Neoplasm Metastasis, 79-6826
Cystadenoma
 Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)- 79-6713
Cystadenoma, Papillary
 Cholanthrene, 3-Methyl-, 79-6826
Estrogens
 Receptors, Hormone, 79-6858
Glucocorticoids
 Precancerous Conditions, 79-6963
Hybrid Cells
 Antigens, Neoplasm, 79-7092
 Histocompatibility Antigens, 79-7071 79-7092
 Immunization, 79-6967
 Transplantation Immunology, 79-7071
L Cells
 Hybrid Cells, 79-6967
LH
 R2323, 79-6857
Lymphoma
 Virus, Moloney Murine Leukemia 79-7071
Papilloma
 Mucopolysaccharides, 79-7199
Progesterone
 LH, 79-6857
 Receptors, Hormone, 79-6857
Prolactin
 1-Piperazineethanol, 4-(3-(2-Chlorophenothiazin-10-yl)propyl)- 79-7198
 Pituitary Grafts, 79-6858
 Receptors, Hormone, 79-6858
 Strain Difference, Mouse, 79-7198
Radiation, Ionizing
 Co-carcinogenic Effect, 79-6847
Reverse Transcriptase
 Virus Cultivation, 79-6966
 4,4'-Stilbenediol, α,α' -Diethyl-

Mammary Neoplasms, Experimental (cont'd)
 Co-carcinogenic Effect, 79-6850
 Tannic Acid
 DNA Replication, 79-6786
 Ultraviolet Rays
 Immune Response, Mouse, 79-6878
 Virus, Murine Leukemia
 Antigens, Viral, 79-6967
 Virus, Murine Mammary Tumor
 Antibodies, Viral, 79-6971
 Antigens, Viral, 79-6967, 79-6972
 Cell Line, 79-6966
 Glucocorticoids, 79-6963
 Horizontal Transmission, 79-6972
 Hybrid Cells, 79-7071
Mandibular Neoplasms
 Fibrosarcoma
 Radiation, Ionizing, 79-6909
 Retinoblastoma
 Radiotherapy, 79-6909
Manganese Chloride
 Azaguanine Resistance
 Mutagenic Activity, 79-6652
Medulloblastoma
 Virus, Polyoma, BK
 Histologic Study, Hamster, 79-7033
Melanoma
 Alanine, 3-(3,4-Dihydroxyphenyl)-
 Melanosomes, Incorporation, 79-7195
 Antigens, Neoplasm
 Horizontal Transmission, 79-7086
 Hypersensitivity, Delayed, 79-7087
 Leukocyte Adherence Inhibition Test 79-7086
 Lymphocytes, 79-7087
 Ethnic Groups
 Epidemiology, Hawaii, 79-7167
 Site Distribution, 79-7167
 Genetics
 Immune Response, 79-7086
 IgG
 Antigen-Antibody Complex, 79-7085
 Latitude
 Epidemiology, 79-7148
MSH
 Adenosine Cyclic 3',5' Monophosphate, 79-7194
 RNA Replication, 79-7194
 Tyrosinase, 79-7194
 Neoplasms, Multiple Primary
 Benz(a)anthracene, 7,12-Dimethyl- 79-6850
Nevus
 Immunologic Deficiency Syndromes 79-7084
 4,4'-Stilbenediol, α,α' -Diethyl-
 Co-carcinogenic Effect, 79-6850
 Transplantation, Homologous
 Graft vs Host Reaction, 79-7089
 Immunity, Cellular, 79-7089
 Ultraviolet Rays
 Co-carcinogenic Effect, Review 79-6625, 79-6628
 Epidemiology, Review, 79-6628
 Pigmentation, 79-7148
Membrane Proteins
 Virus, Adeno 2
 Cells, Cultured, 79-7042
 Virus, Newcastle Disease
 Hemolysis, 79-7061
 Virus, Polyoma
 Cell Transformation, Neoplastic 79-7029
 Virus, Sendai
 Hemolysis, 79-7061
Meningioma
 Brain Neoplasms
 Karyotyping, 79-7099
 Chromosome Aberrations
 Mitosis, 79-7099
 Chromosomes, Human, 21-22
 Monosomy, 79-7099

Meningioma (cont'd)
 Spinal Cord Neoplasms
 Karyotyping, 79-7099
 Virus, SV40
 Antigens, Neoplasm, 79-7039
DL-Menthol
 Dose-Response Study
 Carcinogenic Potential, 79-6660
Mercury, Chloromethyl-
 Ependyoma
 Nitrous Acid, Sodium Salt, 79-6651
 Urea, Ethyl Nitroso-, 79-6651
 Neurilemma
 Nitrous Acid, Sodium Salt, 79-6651
 Urea, Ethyl Nitroso-, 79-6651
 Nitrous Acid, Sodium Salt
 Transplacental Carcinogenesis 79-6651
 Urea, Ethyl Nitroso-
 Transplacental Carcinogenesis 79-6651
Mesenchymoma
 Fibroblasts
 Cell Adhesion, 79-7118
 Hematopoiesis, 79-7118
 Kidney Neoplasms
 Dimethylamine, *N*-Nitroso-, 79-6863
 2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-, 79-6868
 Leukemia, Myelocytic
 Transplantation, Heterologous 79-7118
Mesothelioma
 Asbestos
 Fiber Mixture, Review, 79-6639
 Peritoneal Neoplasms
 Radiation, Ionizing, 79-6913
 Radiation, Ionizing
 Case Report, 79-6913
 Tellurium, Tetrakis(diethylthiocarbamate)-
 Carcinogenic Potential, 79-6658
 α -Toluidine, Hydrochloride
 Carcinogenic Potential, 79-6752
 Urogenital Neoplasms
 α -Toluidine, Hydrochloride, 79-6752
Metalloproteins
 Cadmium Chloride
 Erythrocytes, 79-6645
 Lymphocytes, 79-6645
Metaplasia
 4,4'-Stilbenediol, α,α' -Diethyl-
 Prostate, Mouse, 79-6846
Methane, Azoxy-
 Bile
 Ames Test, 79-6768
 Mutagenic Metabolite, 79-6768
 Intestinal Neoplasms
 Adenocarcinoma, 79-6860
 Dietary Fats, 79-6860
Methane, Triiodo-
 Carcinogenic Potential
 Dose-Response Study, 79-6659
Methanesulfonic Acid, Butyl Ester
 Ames Test
 Azaguanine Resistance, 79-6700
Methanesulfonic Acid, Ethyl Ester
 Mammary Neoplasms, Experimental
 Adenocarcinoma, 79-6649
 Mutagenic Activity
 Thioguanine Resistance, 79-6700
 Mutation
 Colony Formation, 79-7044
 Peptides
 Cell Transformation, Neoplastic 79-7187
Tradescantia paludosa
 Mutagenic Activity, 79-6899

Methanesulfonic Acid, Methyl Ester
Mutagenic Activity
Thioguanine Resistance, 79-6700

Methanesulfonic Acid, Propyl Ester
Mutagenic Activity
Thioguanine Resistance, 79-6700

Methanol, (Methyl-*O*/*N*-azoxy)-, Acetate (Ester)
Bile

Ames Test, 79-6768
Mutagenic Metabolite, 79-6768
Intestinal Neoplasms
Barbituric Acid, 5-Ethyl-5-phenyl-, Sodium Salt, 79-6675

Methomyl, *N*-Nitroso-
Cell Transformation, Neoplastic
Embryo, Hamster, 79-6812

Methotrexate
Chromosome Aberrations
Bone Marrow, 79-6783
Micronucleus Test, 79-6783

Methylamine, *N*-Nitroso-
Ames Test
 α -Acetoxy Derivatives, 79-6732
Mutagenic Activity
 α -Acetoxy Derivatives, 79-6732

Mezerein
Isoproterenol
Adenosine Cyclic 3',5' Monophosphate, 79-6800
Ornithine Decarboxylase
Enzyme Induction, 79-6800
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 79-6800

Microsomes, Liver
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
Metabolism, 79-6757
Benzo(a)pyrene
Carcinogenic Metabolite, 79-6832
Phenol Metabolites, 79-6837
Benzylamine, *N*-Methyl-*N*-nitroso-
Benzaldehyde, 79-6742
Cholanthren-2-ol, 3-Methyl-
DNA Adducts, 79-6828
Cholanthrene, 9,10-Dihydro-9,10-dihydroxy-3-methyl-
DNA Adducts, 79-6828
Cholanthrene, 11,12-Dihydro-11,12-dihydroxy-3-methyl-
DNA Adducts, 79-6828
Cholanthrene, 3-Methyl-
Cycloheximide, 79-6821
DNA Adducts, 79-6828
Dimethylamine, *N*-Nitroso-
Quantitation Method, 79-6734
Ethane, Bromo-
Macromolecules, Binding, 79-6664
Ethane, 1,2-Dibromo-
Macromolecules, Binding, 79-6664
Ethanol, 2-Bromo-
Macromolecules, Binding, 79-6664
Ethanol, *N*-Nitrosoiminodi-
Quantitation Method, 79-6734
Fluoren-2-amine
Ames Test, 79-6842
Phenethylamine, *N,N*-Dimethyl-*N*-nitroso-
Formaldehyde, 79-6742
Phenethylamine, *N*-Methyl-*N*-nitroso-
Acetophenone, 79-6742
Pyrrolidine, 1-Nitroso-
Quantitation Method, 79-6734

Microwaves
Drosophila melanogaster
Mutagenic Activity, 79-6895
Radiation, Non-Ionizing
Mutagenic Activity, 79-6895

Mixed Function Oxidases
Aflatoxin B1

Mixed Function Oxidases (cont'd)
Liver, Rat, 79-6787
Cholanthrene, 3-Methyl-
Cycloheximide, 79-6821

Morpholine, 2,6-Dimethyl-*N*-nitroso-
Digestive System Neoplasms
Hamster, Review, 79-6612
Isomers
Separation Procedure, 79-6745
Pancreatic Neoplasms
Precancerous Conditions, 79-7125
Respiratory Tract Neoplasms
Carcinoma, Bronchogenic, 79-6612
Hamster, Review, 79-6612

Morpholine, *N*-Nitroso-
Respiratory Tract Neoplasms
Carcinoma, Bronchogenic, 79-6612

Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
Neovascularization, 79-6816
Precancerous Conditions, 79-6816
Carbamic Acid, Nitrosopentyl-, Ethyl Ester
Histological Study, Rat, 79-6701
Carcinoma, Epidermoid
Benz(a)anthracene, 7,12-Dimethyl-, 79-6816
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 79-6773
Epidemiology, Review, 79-6640
Ethyl Alcohol, 79-6640
Smoking, 79-6640
Virus, Herpes Simplex 1, 79-6641
Papilloma
Benz(a)anthracene, 7,12-Dimethyl-, 79-6816
Virus, Herpes Simplex 1
Seroepidemiology, Review, 79-6641

MSH
Actinomycin D
Tyrosinase, 79-7194
Cycloheximide
Tyrosinase, 79-7194
Melanoma
Adenosine Cyclic 3',5' Monophosphate, 79-7194
RNA Replication, 79-7194
Tyrosinase, 79-7194

Mucopolysaccharides
Mammary Neoplasms, Experimental
Adenoma, 79-7199
Carcinoma, 79-7199
Papilloma, 79-7199

Multiple Myeloma
Epidemiology
Printers, 79-7176
Lead
Occupational Hazard, 79-7176
Leukemia
Drug Therapy, 79-7155
Sarcoma, Osteogenic
Drug Therapy, 79-6908
Radiation, Ionizing, 79-6908

Muramidase
Leukemia, Myelocytic
Cell Differentiation, 79-6796

Mutagens
DNA Repair
Peptide Hydrolases, Review, 79-6623
Germ Cells
Bioassay, Mouse, 79-7188

Mutation
Carcinogen, Chemical
DNA Repair, Review, 79-6605
Glycine, *N*-(Aminocarbonyl)-*N*-nitroso-
DNA Repair, 79-6706
Escherichia coli, 79-6706
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Colony Formation, 79-7044
Methanesulfonic Acid, Ethyl Ester
Colony Formation, 79-7044

Mutation (cont'd)
Oncogenic Viruses
DNA Repair, Review, 79-6605
Virus, Adeno 5
Colony Formation, 79-7044

Myasthenia Gravis
T-Lymphocytes
Lymphocyte Depletion, 79-7076
Lymphoma
Case Report, 79-7076
Radiotherapy, 79-7076

Mycobacterium butyricum
Arthritis, Adjuvant
Macrophages, 79-7081
Macrophages
Antitumor Activity, 79-7081

Mycosis Fungoides
Hodgkin's Disease
Case Report, 79-7111

Myelofibrosis
Hematopoiesis
Transplantation Model, 79-7118

Myeloproliferative Disorders
Hematopoiesis
Transplantation Model, 79-7118

Myosin
Virus, Rous Sarcoma
Cell Differentiation, 79-6945

NADH, NADPH Oxidoreductases
Stomach Neoplasms
Adenocarcinoma, 79-7128
Carcinoma, Mucinous, 79-7128

1,5-Naphthalenediamine
Gynecologic Neoplasms
Adenoma, 79-6772
Polyps, 79-6772
Sarcoma, 79-6772
Hepatoma
Adenoma, 79-6772
Lung Neoplasms
Adenoma, 79-6772
Sarcoma
Carcinogenic Potential, 79-6772
Thyroid Neoplasms
Adenoma, 79-6772
Carcinoma, Papillary, 79-6772
Cystadenoma, Papillary, 79-6772

2-Naphthylamine
Bladder Neoplasms
Cyclophosphamide, 79-6771
Precancerous Conditions, 79-6771
Carcinoma, Transitional Cell
Cyclophosphamide, 79-6771
Hepatoma
Cyclophosphamide, 79-6771
Urologic Neoplasms
Animal Model, Hamster, 79-6822

1-Naphthylamine, *N*-Hydroxy-
Glucuronates
Microsomal, Urinary Conjugates
79-6767
Uridine Diphosphate Sugars
Metabolism, 79-6767

2-Naphthylamine, *N*-Hydroxy-
Glucuronates
Microsomal, Urinary Conjugates
79-6767
Uridine Diphosphate Sugars
Metabolism, 79-6767

Nasopharyngeal Neoplasms
Environmental Hazard
Epidemiology, Taiwan, 79-7141
Ethnic Groups
Epidemiology, Malaysia, 79-7180
Smoking
Co-carcinogenic Effect, 79-7141
Virus, Epstein-Barr
Antigen-Antibody Reactions, 79-7018
Epidemiology, Taiwan, 79-7141

Nasopharyngeal Neoplasms (cont'd)
Seroepidemiology, Cuba, 79-7018

Necrosis

Benzenediazosulfonic Acid, *p*-(Dimethylamino)-, Sodium Salt
Kidney Tubules, 79-6656

Neoplasm Metastasis

Adenocarcinoma
Transplantation, Homologous, 79-6728

Breast Neoplasms

Antigens, Neoplasm, 79-7093

Carcinoma 256, Walker

Dextrans, 79-6657

Wounds and Injuries, 79-6657

Colonic Neoplasms

Antigens, Neoplasm, 79-7093

Hepatoma

Benzene, 4-Allyl-
1,2-(methylenedioxy)-, 79-6748

Hodgkin's Disease

Subtype, 79-7161

Lung Neoplasms

Adenocarcinoma, 79-6728

Wounds and Injuries, 79-6657

Lymphoma

Macrophages, 79-7077

Radiation, Ionizing, 79-7077

Mammary Neoplasms, Experimental

Cholanthrene, 3-Methyl-, 79-6826

Neoplasm Recurrence, Local

Carcinoma, Basal Cell

Uracil, 5-Fluoro-, 79-6738

Pituitary Neoplasms

Radiation, Ionizing, 79-6902

Neoplasm Regression, Spontaneous

Tracheal Neoplasms

Benz(a)anthracene, 7,12-Dimethyl-, 79-6814

Virus, Moloney Murine Sarcoma

Antibody Formation, 79-7072

Neoplasms (General and Unspecified)

Blood Coagulation Disorders

Musculoskeletal System, 79-7172

Caffeine

Co-carcinogenic Effect, 79-7177

Hemophilia

Epidemiology, 79-7172

Smoking

Co-carcinogenic Effect, 79-7177

Neoplasms, Experimental

Cholanthrene, 3-Methyl-

Immunologic Technics, 79-7066

Concanavalin A

Growth, 79-7080

Hybrid Cells

Antigen-Antibody Complex, 79-7066

Tumorigenicity, Nude Mouse, 79-7067

Immunity, Cellular

Age Factors, Hamster, 79-7064

Macrophages

Immunosuppression, 79-7065

Virus, Adeno 2

Graft vs Host Reaction, 79-7064

Mouse, Nude, 79-7042

Virus, Adeno 12

Deletion Mutants, 79-7050

Virus, CELO

Hamster, 79-7059

Virus, Murine Sarcoma

Immunity, Cellular, 79-7065

Neoplasms, Multiple Primary

Adenocarcinoma

Hodgkin's Disease, 79-7088

Carcinoma, Epidermoid

Hodgkin's Disease, 79-7088

Disgerminoma

Radiation, Ionizing, 79-6913

Hemangioblastoma

Hippel-Lindau Disease, 79-7124

Leukemia, Myeloblastic

Drug Therapy, 79-7105

Radiotherapy, 79-7105

Neoplasms, Multiple Primary (cont'd)

Lung Neoplasms

Chrysene, 1,2-Dihydro-1,2-dihydroxy-, 79-6861

Chrysene, 3,4-Dihydro-3,4-dihydroxy, 79-6861

Chrysene, 1,2-Dihydroxy-3,4-oxy-, 1,2,3,4-tetrahydro-, 79-6861

Melanoma

Benz(a)anthracene, 7,12-Dimethyl-, 79-6850

Pheochromocytoma

Hippel-Lindau Disease, 79-7124

Stomach Neoplasms

Benz(a)anthracene, 7,12-Dimethyl-, 79-6850

Nephritis, Interstitial

Urologic Neoplasms

p-Acetophenetidine, 79-6615

Carcinogen, Environmental, 79-6615

Precancerous Conditions, Review

79-6615

Nephroblastoma

Aniridia

Chromosome Aberrations, 79-7126

Antigens, Neoplasm

Immune Serums, 79-7096

Isolation and Characterization

79-7096

Child

Genetics, Review, 79-6636, 79-6637

Chromosome Aberrations

Chromosomes, Human, 6-12, 79-7126

Chromosomes, Human, 6-12

Glutathione Reductase, 79-7126

Lactate Dehydrogenase, 79-7126

Colonic Neoplasms

Radiotherapy, 79-6918

Dimethylamine, *N*-Nitroso-

Age Factors, Rat, 79-6863

Kidney Neoplasms

Urea, Ethyl Nitroso-, 79-6715

Nitrous Acid, Sodium Salt

Citrulline, 79-6607

Nephrosclerosis

2-Imidazolidinone, 1-(5-Nitro-2-thiazolyl)-

Precancerous Conditions, 79-6868

Nervous System Neoplasms

Neurilemmoma

4,4'-Stilbenediol, α,α' -Diethyl-, 79-6703

Urea, 1-Butyl-1-nitroso-

Transplacental Carcinogenesis, Review

79-6607

Urea, Ethyl-

Nitrous Acid, Sodium Salt, 79-6703

Urea, Ethyl Nitroso-

Gynecologic Neoplasms, 79-6703

Transplacental Carcinogenesis

79-6703

Urea, Methyl Nitroso-

Transplacental Carcinogenesis, Review

79-6607

Urea, *N*-Nitroso-*N*-propyl-

Transplacental Carcinogenesis, Review

79-6607

Neurilemmoma

Ear Neoplasms

Radiation, Ionizing, 79-6901

Nervous System Neoplasms

4,4'-Stilbenediol, α,α' -Diethyl-, 79-6703

Nitrous Acid, Sodium Salt

Mercury, Chloromethyl-, 79-6651

Radiation, Ionizing

Case Report, 79-6901

Urea, Ethyl Nitroso-

Mercury, Chloromethyl-, 79-6651

Neuroblastoma

Benzenamine, 2-Methoxy-5-methyl-

Dose-Response Study, 79-6755

Child

Neuroblastoma (cont'd)

Genetics, Review, 79-6636, 79-6637

Nose Neoplasms

p-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, 79-6750

RNA, Messenger

Poly A, 79-7191

Neuroepithelioma

Eye Neoplasms

Urea, Ethyl Nitroso-, 79-6715

Neurofibroma

Urea, Ethyl Nitroso-

Transplacental Carcinogenesis, Review

79-6607

Neurofibromatosis

Histiocytoma

Case Report, 79-7104

Neuroglia

Dimethylamine, *N*-Nitroso-

Guanine, 7-Methyl-, 79-6704

Purine, 2-Amino-6-methoxy-, 79-6704

Neurons

Urea, Methyl Nitroso-

Guanine, 7-Methyl-, 79-6704

Purine, 2-Amino-6-methoxy-, 79-6704

Neutrophils

Laryngeal Neoplasms

Glucuronidase, 79-7090

Nevus

Melanoma

Immunologic Deficiency Syndromes

79-7084

Nickel

Nose Neoplasms

Occupational Hazard, 79-7143

79-7144, 79-7145

Precancerous Conditions, 79-7143

79-7144, 79-7145

Occupational Hazard

Cigarette Contamination, 79-7145

Nickel Chloride

Azaganine Resistance

Mutagenic Activity, 79-6652

Nickel Sulfide

Rhabdomyosarcoma

Ultrastructural Study, Rabbit, 79-6653

Nicotine, 1'-Demethyl-1'-nitroso-

Respiratory Tract Neoplasms

Carcinoma, 79-6611

Papilloma, 79-6611

Nithiazide

see Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-

Nitric Acid, Plutonium Salt

Dichromic Acid, Dipotassium Salt

Absorption, 79-6923

Nitrosamines

Aniline, Dinitro- (Mixed Isomers)

Food Contamination, 79-6729

Bacillus subtilis

Mutagenic Activity, 79-6732

Dietary Fiber

Binding, 79-6694

Escherichia coli

Mutagenic Activity, 79-6732

Nitrous Acid

Dietary Fiber, 79-6694

Nitrosoacetidine

see Acetic Acid, Ethyl Ester, *N*-

Nitroso-

Nitrous Acid

Gastric Juice

Ames Test, 79-6692

Hexane, 1-Nitro-

Food Contamination, 79-6693

Nitrosamines

Dietary Fiber, 79-6694

Nitrous Acid, Sodium Salt

Citrulline
Transplacental Carcinogenesis, Review
79-6607

Co-carcinogenic Effect
Transplacental Carcinogenesis
79-6651

Ependyoma
Mercury, Chloromethyl-, 79-6651

Mercury, Chloromethyl-
Transplacental Carcinogenesis
79-6651

Nephroblastoma
Citrulline, 79-6607

Nervous System Neoplasms
Urea, Ethyl-, 79-6703

Neurilemmoma
Mercury, Chloromethyl-, 79-6651

Norgestrel

Chromatids
Lymphocytes, 79-6856
Mutagenic Activity, 79-6856

Nose Neoplasms

Adenocarcinoma
Transplacental Carcinogenesis
79-6725

Diethylamine, *N*-Nitroso-
Transplacental Carcinogenesis
79-6725

Neuroblastoma
p-Toluamide, *N*-Isopropyl- α -(2-
methylhydrazino)-, 79-6750

Nickel
Occupational Hazard, 79-7143
79-7144, 79-7145
Precancerous Conditions, 79-7143
79-7144, 79-7145

Smoking
Precancerous Conditions, 79-6838

Nucleosides

Toluene, α -Chloro-
Alkylation, 79-6740

Nutrition

Stomach Neoplasms
Epidemiology, Israel, 79-7183

Occupational Hazard

Colonic Neoplasms
Epidemiology, 79-7176
Ethylene, Chloro-
Chromosome Aberrations, 79-6662

Hodgkin's Disease
Carcinogen, Chemical, 79-7154
Epidemiology, 79-7176
Epidemiology, Sweden, 79-7154

Leukemia
Benzene, 79-7176

Lung Neoplasms
Epidemiology, Louisiana, 79-7179

Multiple Myeloma
Lead, 79-7176

Nickel
Cigarette Contamination, 79-7145

Nose Neoplasms
Nickel, 79-7143, 79-7144, 79-7145

Radiation, Ionizing
Chromosome Aberrations, 79-6910

Skin Diseases
Ethylene, Chloro-, 79-6663

Odontogenic Tumor

Urea, Ethyl Nitroso-
Carcinogenic Activity, Opossum
79-6715

Oncogenic Viruses

Air Pollutants
Co-carcinogenic Effect, Review
79-6617

Cell Transformation, Neoplastic
Cells, Cultured, Review, 79-6617

DNA Repair
Peptide Hydrolases, Review, 79-6623

Mutation
DNA Repair, Review, 79-6605

Oncogenic Viruses (cont'd)

Perinatal Carcinogenesis
Species Difference, Review, 79-6602

Ornithine Decarboxylase

Mezerein
Enzyme Induction, 79-6800

Retinol
Cell Cycle Kinetics, 79-6843

Skin Neoplasms
Hyperplasia, 79-6800

Teleocidin B, Dihydro
13-*cis*-Retinoic Acid, 79-6844

12-*O*-Tetradecanoylphorbol-13-acetate
Cells, Cultured, 79-6793
Enzyme Induction, 79-6800

Orotic Acid

Aflatoxin B1
Metabolism, Gerbil, 79-6788

Osteolysis

Ethylene, Chloro-
Occupational Hazard, 79-6663

Ovarian Neoplasms

Adenocarcinoma
Endometriosis, 79-7133
Genetics, 79-7133

Adenocarcinoma, Papillary
Endometriosis, 79-7133

Benz(a)anthracene, 7,12-Dimethyl-
Castration, Mouse, 79-6810

Transplacental Carcinogenesis
79-6618
Transplantation, Autologous, 79-6810

Theca Cell Tumor
Virus, Cytomegalo, 79-7010

2,4-Oxazolidinedione, 3-(3,5-
Dichlorophenyl)-5,5-dimethyl-
Liver Neoplasms
Acetamide, *N*-Fluorene-2-yl-, 79-6687

2-Oxetanone

Ames Test
Mutagenic Activity, 79-6700
Lymphocytes
Azaguanine Resistance, 79-6700

Oxidoreductases

Benz(a)anthracene, 7,12-Dimethyl-
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
79-6813

Benzenamine, *N,N*-Dimethyl-4-((3-
methylphenyl)azo)-
Chloramphenicol, 79-6757

Oxygen

Benz(a)anthracene, 7,12-Dimethyl-
Photosensitization, 79-6871
Light
Cell Transformation, Neoplastic
79-6894

Pactamycin

Virus, Rous-Associated
Antigenic Determinants, 79-6948

Pancreatic Neoplasms

Adenocarcinoma
Dipropylamine, 2,2'-Dioxo-*N*-nitroso-
79-6728

Carcinoma
Aflatoxin B1, 79-6790

Carcinoma, Ductal
Ultrastructural Study, 79-7125

Dipropylamine, 2-Acetoxy-*N*-nitroso-
Precancerous Conditions, 79-7125

Dipropylamine, 2,2'-Dihydroxy-*N*-
nitroso-
Bile Acids and Salts, 79-6727

Precancerous Conditions, 79-7125
Dipropylamine, 2,2'-Dioxo-*N*-nitroso-
Transplantation, Homologous, 79-6728

Hemangi endothelioma
Aflatoxin B1, 79-6790

Islet Cell Tumor
Guthion, 79-6777

Morpholine, 2,6-Dimethyl-*N*-nitroso-

Pancreatic Neoplasms (cont'd)

Precancerous Conditions, 79-7125

Pentadecane, 2,6,10,14-Tetramethyl-
Hematopoiesis, 79-6672

Immune Response, Hamster, 79-6672

Propylamine, *N*-(2-Oxypropyl)-*N*-
nitroso-
Precancerous Conditions, 79-7125

Sarcoma
Pentadecane, 2,6,10,14-Tetramethyl-
79-6672

Solvents
Air Pollution, 79-7165

Papilloma

Benzo(e)pyrene
Carcinogenic Activity, Mouse, 79-6815

Bladder Neoplasms
Aflatoxin B1, 79-6790

Precancerous Conditions, Rat, 79-6733

Cholanthrene, 3,11-Dimethyl-
12-*O*-Tetradecanoylphorbol-13-acetate
79-6827

Cholanthrene, 3-Methyl-
12-*O*-Tetradecanoylphorbol-13-acetate
79-6827

Esophageal Neoplasms
Carbamic Acid, Diethylthio-, 2-
Chloroallyl Ester, 79-6702

Laryngeal Neoplasms
Diethylamine, *N*-Nitroso-, 79-6725

Mammary Neoplasms, Experimental
Mucopolysaccharides, 79-7199

Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
79-6816

Respiratory Tract Neoplasms
Diethylamine, *N*-Nitroso-, 79-6678

Ethanol, *N*-Nitrosoiminodi-, 79-6611

Nicotine, 1'-Demethyl-1'-nitroso-
79-6611

Piperidine, 1-Nitroso-, 79-6612

Skin Neoplasms
Propene, 1,3-Dichloro-, 79-6666

Stomach Neoplasms
Propene, 3-Chloro-, 79-6669

Tracheal Neoplasms
Diethylamine, *N*-Nitroso-, 79-6725

Paraganglioma

Virus, Papova
DNA, Viral, 79-7020

Isolation and Characterization
79-7020

Virus, RNA Tumor
Isolation and Characterization
79-7020

Penicillin G, Sodium Salt

Cholanthrene, 3-Methyl-
Cell Transformation, Neoplastic
79-6823

Pentadecane, 2,6,10,14-Tetramethyl-

Adrenal Gland Neoplasms
Hyperplasia, 79-6672

Kidney Neoplasms
Hyperplasia, 79-6672

Pancreatic Neoplasms
Hematopoiesis, 79-6672

Immune Response, Hamster, 79-6672

Sarcoma, 79-6672

Pentanoic Acid, 3,5-Dihydroxy-3-methyl-

Adenocarcinoma
Cholesterol, 79-7197

2-Pentanone, 4-Methyl-

Lymphoma
Air Pollution, 79-7165

Peptides

Benz(a)anthracene, 7,12-Dimethyl-
Cell Transformation, Neoplastic
79-6809

Carcinoma

Virus, Herpes Simplex 2, 79-7008

Cell Transformation, Neoplastic
Growth Substances, 79-7187

Peptides (cont'd)

Lymphoma
Virus, Murine Mammary Tumor
79-6965

Methanesulfonic Acid, Ethyl Ester
Cell Transformation, Neoplastic
79-7187

Phorbol 12,13-Didecanoate
Binding, 79-6809
12-*O*-Tetradecanoylphorbol-13-acetate
Binding, 79-6799, 79-6809

Virus, Adeno 2
Genes, Viral, 79-7043

Virus, Adeno 5
RNA, Messenger, 79-7045
Virus, Murine Mammary Tumor
Protein Kinase, 79-6962

Peritoneal Neoplasms

Mesothelioma
Radiation, Ionizing, 79-6913

Petroleum

Adrenal Gland Neoplasms
Hyperplasia, 79-6672
Giant Cell Tumors
Immune Response, Hamster, 79-6672
Hepatoma
Immune Response, Hamster, 79-6672
Kidney Neoplasms
Hyperplasia, 79-6672

Peutz-Jeghers Syndrome

Gastrointestinal Neoplasms
Adenocarcinoma, 79-7130
Carcinoma, 79-7130

Phagocytosis

Leukemia, Myelocytic
Cell Differentiation, 79-6796
12-*O*-Tetradecanoylphorbol-13-acetate
79-6794

Pharyngeal Neoplasms

Carbamic Acid, Nitrosopentyl-, Ethyl Ester
Structure-Activity Relationship
79-6701
Carcinoma, Epidermoid
Epidemiology, Review, 79-6640
Ethyl Alcohol, 79-6640
Radiation, Ionizing, 79-6912, 79-7140
Epidemiology
Greenland, 79-7151
Radiation, Ionizing
Case Report, 79-6912
Epidemiology, 79-7140

Phenanthrene, 1,2-Dihydro-3,4-oxy-1,2,3,4-tetrahydro-

Lung Neoplasms
Carcinogenic Activity, Mouse, 79-6861

Phenethylamine, *N*, α -Dimethyl-*N*-nitroso-

Formaldehyde
Microsomes, Liver, 79-6742
Microsomes
Metabolism, Rat, 79-6742

Phenethylamine, *N*-Methyl-*N*-nitroso-

Acetophenone
Microsomes, Liver, 79-6742
Formaldehyde
Barbituric Acid, 5-Ethyl-5-phenyl-
79-6742
Microsomes
Metabolism, Rat, 79-6742

Phenol, *o*-Bromo-

Barbituric Acid, 5-Ethyl-5-phenyl-
Metabolism, Liver, 79-6746

Phenol, *p*-Bromo-

Barbituric Acid, 5-Ethyl-5-phenyl-
Metabolism, Liver, 79-6746

Phenol, 4,4'-(1,2-Diethylene)di-, meso-

Gynecologic Neoplasms
Carcinoma, 79-7174

Phenol, (1,1-Dimethylethyl)-4-methoxy-
Benzo(a)pyrene
DNA, Binding, 79-6832

Phenol, Pentachloro-
Dibenzo-*p*-dioxin, 2,7-Dichloro-
Environmental Hazard, 79-6774

Phenol, 2,4,6-Trichloro-

Hepatoma
Dose-Response Study, 79-6747
Leukemia
Dose-Response Study, 79-6747
Liver Neoplasms
Adenoma, 79-6747
Lymphoma
Dose-Response Study, 79-6747

Phenothiazines

Photosensitization
Dosimeters, 79-6892

***p*-Phenylenediamine, 2-Chloro-, Sulfate**

Hepatoma
Carcinogenic Potential, 79-6759
Kidney Neoplasms
Carcinogenic Potential, 79-6759
Hyperplasia, 79-6759

Pheochromocytoma

Adrenal Gland Neoplasms
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-, 79-6690
o-Toluidine, 5-Chloro-, 79-6751
Neoplasms, Multiple Primary
Hippel-Lindau Disease, 79-7124
o-Toluidine, 5-Chloro-
Dose-Response Study, 79-6751

Phorbol 12,13-Didecanoate

Actin
Fibroblasts, 79-6797
Peptides
Binding, 79-6809

Phorbol Esters

Leukemia, Myelocytic
Cell Differentiation, 79-6796

Phosphamidon

Splenic Neoplasms
Angiosarcoma, 79-6655
Hemangioma, 79-6655
Thyroid Neoplasms
Adenoma, 79-6655
Carcinogenic Potential, 79-6655
Carcinoma, 79-6655

Phosphine Sulfide, Tris(1-aziridinyl)-

Ames Test
Mutagenic Activity, 79-6785

Phosphogluconate Dehydrogenase

Acetamide, *N*-Fluoren-2-yl-
Enzymatic Activity, 79-6682

Phosphoproteins

Adenocarcinoma
Virus, Murine Mammary Tumor
79-6962
Virus, Adeno 12
IgG, 79-7047
Virus, Avian Sarcoma
Antibody Specificity, 79-6935
Antigenic Determinants, 79-6935
Cell Transformation, Neoplastic
79-6936
Protein Kinase, 79-6936, 79-6937
Vertebrate Cells, 79-6937
Virus, B77
Antibody Specificity, 79-6935
Virus, Rauscher Murine Leukemia
Amino Acids, 79-6990

Phosphoric Acid, Tris(*p*-nitrophenyl) Ester

Acetohydroxamic Acid, *N*-Fluoren-2-yl-
Mutagenic Activity, 79-6681

Phosphorofluoric Acid, Bis(1-methylethyl) Ester

DNA, Alkylation, 79-6865

Phosphorothioic Acid, *O*,*O*-Diethyl *O*-(*p*-

Nitrophenyl) Ester
Adrenal Gland Neoplasms
Adenoma, 79-6765
Carcinoma, 79-6765
Dose-Response Study, 79-6765

Phosphorothioic Acid, *O*,*O*-Dimethyl *O*-(*p*-

Nitrophenyl) Ester
Dose-Response Study
Carcinogenic Potential, 79-6741

Phosphotransferases, ATP

Virus, Avian Sarcoma
Tosyllysine Chloromethyl Ketone
79-6933

Photosensitization

Phenothiazines
Dosimeters, 79-6892

Phthalic Anhydride

Lung Neoplasms
Adenoma, 79-6762
Carcinogenic Potential, 79-6762
Lymphoma
Carcinogenic Potential, 79-6762

Pigmentation

Melanoma
Ultraviolet Rays, 79-7148

1-Piperazineethanol, 4-(3-(2-

Chlorophenothiazin-10-yl)propyl)-
Mammary Neoplasms, Experimental
Prolactin, 79-7198

Piperidine, 3,5-Dimethyl-1-nitroso-

Isomers
Separation Procedure, 79-6745

Piperidine, 1-Nitroso-

Respiratory Tract Neoplasms
Carcinoma, Bronchogenic, 79-6612
Papilloma, 79-6612
Transplacental Carcinogenesis
Hamster, 79-6721

Pituitary Neoplasms

Adenoma
Anthraquinone, 1-Amino-2-methyl-
79-6792
Adenoma, Chromophobe
Radiation Effects, 79-6902
Radiation, Ionizing
Neoplasm Recurrence, Local, 79-6902
4,4'-Stilbenediol, α,α' -Diethyl-
Carcinogenic Activity, Rat, 79-6847

Plant Agglutinins

Virus, Rous Sarcoma
Lymphocyte Transformation, 79-6952

Plant Tumors

Radiation, Ionizing
Cells, Cultured, 79-6898
Haworthia mirabilis, 79-6898

Plasmacytoma

Actinomycin D
Polyribosomes, 79-7192
Concanavalin A
Immune Response, 79-7080
Hybrid Cells
A-Type Particles, 79-7055

IgG

Polyribosomes, 79-7192
RNA, Messenger, 79-7192

Lymphocytes

A-Type Particles, 79-7055
Proteins
Temperature, 79-7192

Virus, C-Type RNA Tumor

Viral Proteins, 79-6993

Virus-Like Particles

Cell Transformation, Neoplastic
79-7055

Virus, Murine Leukemia

A-Type Particles, 79-7053

Plasmacytoma (cont'd)
 Virus, Myeloma-Associated
 A-Type Particles, 79-7053, 79-7054
 Virus, RNA Tumor
 Virus-Like Particles, 79-7054

Plasmodium berghei yoelii
 Virus, SV40
 Immunosuppression, 79-7041

Plutonium
 Citric Acid, Iron Salt
 Adsorption, 79-6924
 Dichromic Acid, Dipotassium Salt
 Absorption, 79-6923
 Gastrointestinal System
 Absorption, 79-6923
 Adsorption, 79-6924

Plutonium Dioxide
 Lung Neoplasms
 Inhalation Study, Hamster, 79-6921

Polonium
 Lung Neoplasms
 Adenocarcinoma, 79-6922
 Carcinoma, Epidermoid, 79-6922
 Iron Oxide, 79-6922

Poly A
 Benz(a)anthracene, 7,12-Dimethyl-
 Binding, 79-6807
 Benzo(a)pyrene
 Binding, 79-6807
 Dibenz(a,c)anthracene
 Binding, 79-6807
 Dibenz(a,h)anthracene
 Binding, 79-6807
 Neuroblastoma
 RNA, Messenger, 79-7191
 RNA, Messenger
 Actin, 79-7191
 Histones, 79-7191
 Tubulin, 79-7191
 Virus, Moloney Murine Leukemia
 RNA, Viral, 79-6985

Polycyclic Hydrocarbons
 Aryl Hydrocarbon Hydroxylases
 Lymphocytes, 79-6819
 Cell Transformation, Neoplastic
 Cells, Cultured, Review, 79-6617

Polycthemia
 Virus, Friend Murine Leukemia
 Virus, Helper, 79-6976

Polyps
 Gastrointestinal Neoplasms
 Genetics, 79-7130
 Gynecologic Neoplasms
 1,5-Naphthalenediamine, 79-6772
 Laryngeal Neoplasms
 Diethylamine, *N*-Nitroso-, 79-6725
 Tracheal Neoplasms
 Diethylamine, *N*-Nitroso-, 79-6725
 Uterine Neoplasms
 1,1'-Biphenyl, 4,4'-Diisocyanato-
 3,3'-dimethoxy-, 79-6769

Polyribosomes
 L Cells
 Actinomycin D, 79-7192
 Plasmacytoma
 Actinomycin D, 79-7192
 IgG, 79-7192
 Virus, B77
 RNA, Viral, 79-6954
 Virus, Moloney Murine Leukemia
 RNA, Viral, 79-6985

Porphyrins
 Acetic Acid, (2,4,5-Trichlorophenoxy)-
 Metabolism, 79-6677

Precancerous Conditions
 Benzenamine, *N,N*-Dimethyl-4-((3-
 methylphenyl)azo)-
 Liver, Rat, 79-6756
 Bladder Neoplasms

Precancerous Conditions (cont'd)
 2-Naphthylamine, 79-6771
 Carcinoma, Bronchogenic
 Histological Study, Hamster, Review
 79-6638

Carcinoma, Transitional Cell
 1-Butanol, 4-(Butylnitrosamino)-
 79-6731

Cervix Neoplasms
 Epidemiology, Colombia, 79-7185
 Gynecologic Neoplasms

Estradiol, 79-6852
 4,4'-Stilbenediol, α,α' -Diethyl-
 79-6852

Hepatoma
 Acetamide, *N*-Fluoren-2-yl-, 79-7123
 Diethylamine, *N*-Nitroso-, 79-7123

Intestinal Neoplasms

Adenocarcinoma, 79-6673

Laryngeal Neoplasms

Glucuronidase, 79-7090

Smoking, 79-6845

Leukemia

Anemia, Sideroblastic, 79-7164

Virus, Friend Murine Leukemia

79-6976

Liver Neoplasms

Acetamide, *N*-Fluoren-2-yl-, 79-6687

Iron Accumulation, 79-6688

Serine, Diazoacetate (Ester), 79-6683

Mammary Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-

79-6818, 79-6963

Glucocorticoids, 79-6963

Mouth Neoplasms

Benz(a)anthracene, 7,12-Dimethyl-

79-6816

Nephrosclerosis

2-Imidazolidinone, 1-(5-Nitro-2-
 thiazolyl)-, 79-6868

Nose Neoplasms

Nickel, 79-7143, 79-7144, 79-7145

Smoking, 79-6838

Pancreatic Neoplasms

Dipropylamine, 2-Acetoxy-*N*-nitroso-

79-7125

Dipropylamine, 2,2'-Dihydroxy-*N*-
 nitroso-, 79-7125

Morpholine, 2,6-Dimethyl-*N*-nitroso-

79-7125

Propylamine, *N*-(2-Oxypropyl)-*N*-
 nitroso-, 79-7125

Respiratory Tract Neoplasms

Histological Study, Hamster, Review

79-6638

Stomach Neoplasms

Gastrectomy, 79-7129

Thyroid Neoplasms

Cyanamide, Calcium Salt, 79-6647

Tracheal Neoplasms

Adenocarcinoma, 79-6710

Benz(a)anthracene, 7,12-Dimethyl-

79-6802, 79-6814

Carcinoma, 79-6710

Carcinoma, Epidermoid, 79-6710

Vaginal Neoplasms

5 α -Androstan-3-one, 17 β -Hydroxy-

79-6853

Estradiol, 79-6853

Testosterone, Propionate, 79-6853

Prednisone

Leukemia

Epidemiology, 79-7155

**Pregn-4-ene-3,20-dione, 17-(Acetyloxy)-6 α -
 methyl-**

Uterine Neoplasms

Adenocarcinoma, 79-6854

Progestational Hormones

Uterine Neoplasms

Endometrial Hyperplasia, 79-7173

Epidemiology, 79-7173

Progesterone

Mammary Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-

Progesterone (cont'd)

Benz(a)anthracene, 7,12-Dimethyl-

79-6857

LH, 79-6857

Receptors, Hormone, 79-6857

Prolactin

Benz(a)anthracene, 7,12-Dimethyl-

Estrus, Rat, 79-6811

Mammary Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-

79-6818

1-Piperazineethanol, 4-(3-(2-
 Chlorophenothiazin-10-yl)propyl)-

79-7198

Pituitary Grafts, 79-6858

Receptors, Hormone, 79-6858

Strain Difference, Mouse, 79-7198

Testicular Neoplasms

Leydig Cell Tumor, 79-7137

Virus, Murine Mammary Tumor

RNA, Viral, 79-6963

Propane, 1-Chloro-2,3-epoxy-

Chromosome Aberrations

Quantitation Method, 79-6744

Propane, 1,2-Dibromo-3-chloro-

DNA Repair

Germ Cells, Mouse, 79-6668

Lung Neoplasms

Carcinogenic Activity, Mouse, 79-6666

Skin Neoplasms

12-*O*-Tetradecanoylphorbol-13-acetate

79-6666

Stomach Neoplasms

Carcinogenic Activity, Mouse, 79-6666

Propane, 1,2-Epoxy-

Chromosome Aberrations

Quantitation Method, 79-6744

1-Propanol, 2-Chloro-

Sarcoma

Carcinogenic Activity, Mouse, 79-6666

**1-Propanone, 2-Methyl-1,2-di-3-pyridyl-,
 Tartrate**

Aryl Hydrocarbon Hydroxylases

Lymphocytes, 79-6819

Propene, 1-Chloro-

Stomach Neoplasms

Carcinogenic Activity, Mouse, 79-6666

Propene, 3-Chloro-

Skin Neoplasms

12-*O*-Tetradecanoylphorbol-13-acetate

79-6666

Stomach Neoplasms

Carcinogenic Potential, 79-6669

Carcinoma, Epidermoid, 79-6669

Papilloma, 79-6669

Propene, 1,3-Dichloro-

Lung Neoplasms

Carcinogenic Activity, Mouse, 79-6666

Skin Neoplasms

Papilloma, 79-6666

Stomach Neoplasms

Carcinogenic Activity, Mouse, 79-6666

2-Propenoic Acid, 3-(5-Nitro-2-furyl)-

DNA Replication

Fibroblasts, 79-6697

RNA Replication

Uridine Incorporation, 79-6697

Propiophenone, *p*-Hydroxy-

4,4'-Stilbenediol, α,α' -Diethyl-

Biliary, Urinary Metabolites, 79-6851

Propylamine, *N*-Methyl-*N*-nitroso-

Transplacental Carcinogenesis

Hamster, 79-6721

Propylamine, *N*-(2-Oxypropyl)-*N*-nitroso-

Pancreatic Neoplasms

Precancerous Conditions, 79-7125

Prostaglandins E

Benz(a)anthracene, 7,12-Dimethyl-

- Prostaglandins E (cont'd)**
 DNA, Binding, 79-6803
 Granulocytes
 Colony Stimulating Factor, 79-7073
 Macrophages
 Colony Stimulating Factor, 79-7073
 12-*O*-Tetradecanoylphorbol-13-acetate
 Benzoic Acid, 2-(Acetyloxy)-, 79-6795
 Epidermis, Mouse, 79-6798
 Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-, 79-6795
- Prostaglandins F**
 Breast Neoplasms
 Transferrin, 79-7200
 12-*O*-Tetradecanoylphorbol-13-acetate
 Epidermis, Mouse, 79-6798
- Prostatic Hypertrophy**
 Virus, RNA Tumor
 Reverse Transcriptase, 79-7052
 Virus-Like Particles, 79-7052
- Prostatic Neoplasms**
 Adenocarcinoma
 Reverse Transcriptase, 79-7052
 Marital Status
 Epidemiology, 79-7178
 Steroids
 Diet, 79-7175
 Virus, RNA Tumor
 Virus-Like Particles, 79-7052
- Protein Kinase**
 Virus, Adeno 12
 Antigens, Neoplasm, 79-7047
 Virus, Avian Sarcoma
 Phosphoproteins, 79-6936, 79-6937
 Virus, Murine Mammary Tumor
 Peptides, 79-6962
- Protein Methylase I**
see Protein Arginine Methyltransferase
- Proteins**
 L Cells
 Temperature, 79-7192
 Plasmacytoma
 Temperature, 79-7192
- Psoralen, 8-Methoxy-**
 Skin Neoplasms
 Ultraviolet Rays, 79-6872
 Ultraviolet Rays
 DNA Cross-Links, 79-6872
- Pulmonary Fibrosis**
 Asbestos
 Histocompatibility Antigens, 79-6650
- Purine, 2-Amino-6-ethoxy-**
 Diethylamine, *N*-Nitroso-
 DNA, Alkylation, 79-6862
 DNA Repair, 79-6724
 Liver, Rat, 79-6724, 79-6862
- Purine, 2-Amino-6-methoxy-**
 Acetic Acid, Methylnitrosaminomethyl Ester
 Organ Specificity, 79-6865
 Dimethylamine, *N*-Nitroso-
 Neuroglia, 79-6704
 Triazene, 3,3-Dimethyl-1-phenyl-
 Perinatal Carcinogenesis, 79-6709
 Urea, Methyl Nitroso-
 Neurons, 79-6704
 Perinatal Carcinogenesis, 79-6709
- Purpurogallan**
see 5*H*-Benzocyclohepten-5-one, 2,3,4,6-Tetrahydroxy-
- Pyrene**
 Skin Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6815
- Pyrogallol**
 Ames Test
 Mutagenic Activity, 79-6784
- Pyrrolidine, 1-Nitroso-**
 Body Fluids
 Quantitation Method, 79-6734
 Carcinogenic Activity
 Hamster, Review, 79-6612
 Microsomes, Liver
 Quantitation Method, 79-6734
- Quartz**
 Benzo(a)pyrene
 Transport, Microsomes, 79-6831
- Quinoline, 7-Chloro-4-((4-(diethylamino)-1-methylbutyl)amino)-**
 Skin Neoplasms
 Ultraviolet Rays, 79-6876
- Quinoline, 4-Nitro-, 1-Oxide-**
 Chromosome Aberrations
 Quantitation Method, 79-6744
 DNA
 Carcinogenic Metabolite, 79-6743
- p*-Quinone Dioxime**
see p-Benzoquinone Dioxime
- R2323**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6857
 LH, 79-6857
- Radiation**
 DNA Repair, Review, 79-6605
- Radiation, Ionizing**
 Benzo(a)pyrene
 Mathematical Model, 79-7159
 Brain Neoplasms
 Case Report, 79-6902
 Fibrosarcoma, 79-6902
 Carcinoma, Basal Cell
 Case Report, 79-6905
 Carcinoma, Ehrlich Tumor
 Growth, 79-6906
 Leukocytosis, Tissue, 79-6906
 Cell Transformation, Neoplastic
 Dose-Response Study, 79-6897
 Fibroblasts, Review, 79-6630
 Mathematical Model, 79-6897
 Chromosome Aberrations
 Case Report, 79-6910
 Occupational Hazard, 79-6910
 Colonic Neoplasms
 Adenocarcinoma, 79-6918
 Disgerminoma
 Neoplasms, Multiple Primary, 79-6913
 DNA
 Double Strand Breaks, 79-6904
 DNA Repair
 Chromosome Aberrations, 79-6629
 Ear Neoplasms
 Neurilemmoma, 79-6901
 Erythropoiesis
 Bone Marrow, Spleen, 79-6914
 Fibrosarcoma
 Case Report, 79-6909
 Cholanthrene, 3-Methyl-, 79-6907
 Neoplasm Metastasis, 79-7083
 Neoplasm Recurrence, 79-6907
 Transplantation Immunology, 79-6907
 Gentamicin
 Cell Transformation, Neoplastic
 79-6823
 Hematopoietic Stem Cells
 Blood Cell Count, 79-6914
 Immune Serums
 Blocking Factors, 79-6916
 Immunity, Cellular
 Hamster, 79-6915
 Intestinal Neoplasms
 Adenocarcinoma, 79-6916, 79-6917
 Carcinoma, Mucinous, 79-6917
 Immunity, Cellular, 79-6916
 Laryngeal Neoplasms
 Carcinoma, Epidermoid, 79-7140
 Dental X-Rays, 79-7181
 Epidemiology, 79-7140
 Leukemia L1210
- Radiation, Ionizing (cont'd)**
 DNA Repair, 79-6904
 Leukemia, Radiation-Induced
 Theoretical Model, Mouse, 79-6903
 Viral Proteins, 79-6903
 Liver Neoplasms
 Hamster, 79-6915
 Virus-Like Particles, 79-6915
 Lymphoma
 Neoplasm Metastasis, 79-7077
 Mammary Neoplasms, Experimental
 Adenofibroma, 79-6847
 Co-carcinogenic Effect, 79-6847
 Mandibular Neoplasms
 Fibrosarcoma, 79-6909
 Mesothelioma
 Case Report, 79-6913
 Neurilemmoma
 Case Report, 79-6901
 Peritoneal Neoplasms
 Mesothelioma, 79-6913
 Pharyngeal Neoplasms
 Carcinoma, Epidermoid, 79-6912
 79-7140
 Case Report, 79-6912
 Epidemiology, 79-7140
 Pituitary Neoplasms
 Neoplasm Recurrence, Local, 79-6902
 Plant Tumors
 Cells, Cultured, 79-6898
Haworthia mirabilis, 79-6898
 Sarcoma, Osteogenic
 Case Report, 79-6908
 Multiple Myeloma, 79-6908
 Skin Diseases
 Radiation Injuries, 79-6910
 Splenic Neoplasms
 Hamster, 79-6915
 Virus-Like Particles, 79-6915
 4,4'-Stilbenediol, α,α' -Diethyl-
 Co-carcinogenic Effect, 79-6847
 Thyroid Neoplasms
 Adenocarcinoma, 79-7140
 Carcinoma, 79-7166
 Carcinoma, Papillary, 79-6901
 Epidemiology, 79-7140
Tradescantia paludosa
 Mutagenic Activity, 79-6899
 Ultraviolet Rays
 Co-carcinogenic Effect, 79-6891
 Virus Activation
 Hamster, 79-6915
 Virus, C-Type RNA Tumor
 Antipain, 79-6893
 Virus Activation, 79-6893
 Virus Replication, 79-7056
 Xeroderma Pigmentosum
 Chromosome Aberrations, 79-6629
 DNA Repair, 79-6629
- Radiation, Non-Ionizing**
 Microwaves
 Mutagenic Activity, 79-6895
- Radioisotopes**
 Lung Neoplasms
 Carcinoma, Epidermoid, 79-6896
 Rhodium, 79-6896
 Ruthenium, 79-6896
- Radiotherapy**
 Leukemia, Myeloblastic
 Neoplasms, Multiple Primary, 79-7105
- Raynaud's Disease**
 Ethylene, Chloro-
 Occupational Hazard, 79-6663
- Receptors, Hormone**
 Mammary Neoplasms, Experimental
 Estrogens, 79-6858
 Progesterone, 79-6857
 Prolactin, 79-6858
- Rectal Neoplasms**
 Epidemiology
 Brewery Workers, 79-7184

Respiratory Tract Neoplasms

- Adenocarcinoma
 - 1*H*-Azepine, Hexahydro-1-nitroso-79-6612
 - Azocine, Octahydro-1-nitroso-79-6612
 - Benzo(a)pyrene, 79-6678
- Adenoma
 - Benzo(a)pyrene, 79-6678
 - Diethylamine, *N*-Nitroso-, 79-6678
- Carcinoma
 - Ethanol, *N*-Nitrosoiminodi-, 79-6611
 - Nicotine, 1'-Demethyl-1'-nitroso-79-6611
- Carcinoma, Bronchogenic
 - Morpholine, 2,6-Dimethyl-*N*-nitroso-79-6612
 - Morpholine, *N*-Nitroso-, 79-6612
 - Piperidine, 1-Nitroso-, 79-6612
- Diallylamine, *N*-Nitroso-Hamster, Review, 79-6610
- Marital Status
- Epidemiology, 79-7178
- Morpholine, 2,6-Dimethyl-*N*-nitroso-Hamster, Review, 79-6612
- Papilloma
 - Diethylamine, *N*-Nitroso-, 79-6678
 - Ethanol, *N*-Nitrosoiminodi-, 79-6611
 - Nicotine, 1'-Demethyl-1'-nitroso-79-6611
 - Piperidine, 1-Nitroso-, 79-6612
- Precancerous Conditions
 - Histological Study, Hamster, Review 79-6638
- Smoking
 - Animal Model, Hamster, Review 79-6611
- Tannic Acid
 - Carcinogenic Potential, 79-6786
- Vinylamine, *N*-Ethyl-*N*-nitroso-Hamster, Review, 79-6610

Retinal

- Growth
- Cells, Cultured, 79-6843

Retinoblastoma

- Child
 - Genetics, Review, 79-6636, 79-6637
- Chromosome Aberrations
- Chromosomes, Human, 13-15, 79-7102
- Lymphocytes, 79-7101
- Fibroblasts
 - Radiosensitivity, 79-7102
- Genetics
 - Age Factors, 79-7100
 - Bilateral Tumor, 79-7100
- Mandibular Neoplasms
- Radiotherapy, 79-6909

Retinoic Acid

- Growth
- Cells, Cultured, 79-6843
- Skin Neoplasms
- Ultraviolet Rays, 79-6889

13-*cis*-Retinoic Acid

- Teleocidin B, Dihydro
- Ornithine Decarboxylase, 79-6844

Retinol

- Abnormalities
 - Hamster, 79-6900
- Adriamycin
 - Ames Test, 79-6842
- Fluoren-2-amine
 - Ames Test, 79-6842
- Growth
 - Cells, Cultured, 79-6843
- Hyperthermia
 - Teratogenic Interactions, 79-6900
- Ornithine Decarboxylase
 - Cell Cycle Kinetics, 79-6843

Retinol Acetate

- Growth
- Cells, Cultured, 79-6843
- Hyperplasia
- Estradiol, 79-6853

Retinol Palmitate

- Laryngeal Neoplasms
- Smoking, 79-6845

Reverse Transcriptase

- Mammary Neoplasms, Experimental
- Virus Cultivation, 79-6966
- Prostatic Hypertrophy
 - Virus, RNA Tumor, 79-7052
- Prostatic Neoplasms
 - Adenocarcinoma, 79-7052
- Virus, Avian Sarcoma
 - Temperature Sensitive Mutants 79-6934

Rhabdomyosarcoma

- Fenthion
 - Dose-Response Study, 79-6654
- Nickel Sulfide
 - Ultrastructural Study, Rabbit, 79-6653

Rhinitis

- Smoking
 - Histological Study, Hamster, 79-6838

Rhodium

- Lung Neoplasms
- Radioisotopes, 79-6896

Ribonuclease

- Virus, Avian Sarcoma
 - Temperature Sensitive Mutants 79-6934

Ribonucleotides

- Virus, Herpes Simplex 1
 - Adenosine, 3'-Deoxy-, 79-7006
 - DNA Replication, 79-7006

RNA

- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 - Liver, Rat, 79-6756
 - Nucleotide Sequence, 79-6756

RNA, Messenger

- Alpha Fetoproteins
 - Isolation and Characterization 79-7094
- Hepatoma
 - Alpha Fetoproteins, 79-7094
- Neuroblastoma
 - Poly A, 79-7191
- Plasmacytoma
 - IgG, 79-7192
- Poly A
 - Actin, 79-7191
 - Histones, 79-7191
 - Tubulin, 79-7191
- Virus, Adeno 5
 - Nucleotide Sequence, 79-7045
 - Peptides, 79-7045
- Virus, B77
 - Nucleotide Sequence, 79-6954
- Virus, Moloney Murine Leukemia
 - RNA, Viral, 79-6985
- Virus, Polyoma
 - Deletion Mutants, 79-7023
 - DNA-RNA Hybridization, 79-7022
 - 79-7027
 - DNA, Viral, 79-7024
- Virus, Rat Leukemia
 - Stress, Anaerobic, 79-6994
 - Virus Replication, 79-6994
- Virus, SV40
 - Antigens, Neoplasm, 79-7034

RNA Polymerase

- Sarcoma
 - Virus, Rous Sarcoma, 79-6938
- Virus, Rous Sarcoma
 - DNA Replication, 79-6938
 - Isolation and Characterization 79-6938

RNA Replication

- Melanoma
 - MSH, 79-7194
- 2-Propenoic Acid, 3-(5-Nitro-2-furyl)-
 - Uridine Incorporation, 79-6697

RNA Replication (cont'd)

- 12-*O*-Tetradecanoylphorbol-13-acetate
- Actin, 79-6797

RNA, Ribosomal

- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 79-7016

RNA, Viral

- Benz(a)anthracene, 7,12-Dimethyl-
 - Virus, Murine Mammary Tumor 79-6969
- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 79-7016
- Reverse Transcription
 - Theoretical Model, 79-6984
- Virus, AKR Murine Leukemia
 - DNA-RNA Hybridization, 79-6989
- Virus, Avian Leukemia
 - DNA-RNA Hybridization, 79-6928
 - Nucleotide Sequence, 79-6930
 - Replication-Defective Mutants 79-6928
- Virus, Avian Myelocytomatosis
 - Nucleotide Sequence, 79-6930
- Virus, Helper, 79-6930
- Virus, B77
 - Polyribosomes, 79-6954
- Virus, Epstein-Barr
 - DNA-RNA Hybridization, 79-7016
- Virus, MC29
 - Nucleotide Sequence, 79-6930
 - 79-7060
- Virus, Moloney Murine Leukemia
 - DNA Replication, 79-6984
 - DNA-RNA Hybridization, 79-6986
 - 79-6989
- Liver Regeneration, 79-6986
- Poly A, 79-6985
- Polyribosomes, 79-6985
- Reverse Transcription, 79-6984
- RNA, Messenger, 79-6985
- Virus, Murine Leukemia
 - Liver Regeneration, 79-6986
- Virus, Murine Mammary Tumor
 - Glucocorticoids, 79-6963
 - Prolactin, 79-6963
- Virus, Polyoma
 - DNA-RNA Hybridization, 79-7027

Ruthenium

- Lung Neoplasms
- Radioisotopes, 79-6896

Saccharomyces cerevisiae

- Ultraviolet Rays
- Mutagenic Activity, 79-6869

Salivary Gland Neoplasms

- Adenocarcinoma
 - Virus, Herpes Simplex 1, 79-7007
- Epidemiology
- Greenland, 79-7151

Salmonella typhimurium

- 5*H*-Benzocyclohepten-5-one, 2,3,4,6-Tetrahydroxy-
 - Colicins, 79-6784

Sarcoma

- Benzo(a)pyrene
 - Gamma Globulins, 79-6839
 - Serum Albumin, 79-6839
- Cholanthrene, 3-Methyl-
 - Lymphocyte Culture Test, Mixed 79-7070
- T-Lymphocytes, 79-7082
- Fenthion
 - Dose-Response Study, 79-6654
- Gynecologic Neoplasms
 - 1,5-Naphthalenediamine, 79-6772
- Hybrid Cells
 - Microfilaments, 79-7067
- Liver Neoplasms
 - Hycanthone Methanesulfonate 79-6779
- Virus, SV40, 79-7041
- T-Lymphocytes
 - Growth, 79-7082

Sarcoma (cont'd)
 Suppressor Cells, 79-7082
 1,5-Naphthalenediamine
 Carcinogenic Potential, 79-6772
 Pancreatic Neoplasms
 Pentadecane, 2,6,10,14-Tetramethyl-
 79-6672
 1-Propanol, 2-Chloro-
 Carcinogenic Activity, Mouse, 79-6666
 Splenic Neoplasms
 α -Toluidine, Hydrochloride, 79-6752
 Virus, SV40, 79-7041
 Ultraviolet Rays
 Immune Response, Mouse, 79-6878
 Uterine Neoplasms
 Benzenediazosulfonic Acid, *p*-(Dimethylamino)-, Sodium Salt, 79-6656
 Virus, DNA Tumor
 Carcinogenic Activity, Hamster
 79-7051
 Virus, Moloney Murine Leukemia
 T-Lymphocytes, 79-7082
 Virus, Moloney Murine Sarcoma
 Anti-Antibodies, 79-6988
 Virus, Murine Sarcoma
 Immunosuppression, 79-6960
 Virus, Rous Sarcoma
 Immunologic Techniques, 79-6942
 RNA Polymerase, 79-6938
 Virus, SV40
 Histocompatibility Antigens, 79-7040
 Liver Neoplasms, 79-7041

Sarcoma, Granulocytic
see Leukemia, Myelocytic

Sarcoma, Immunoblastic
see Sarcoma, Reticulum Cell

Sarcoma Kaposi's
 Amyloidosis
 Case Report, 79-7114
 Hematologic Diseases
 Case Report, 79-7114
 B-Lymphocytes
 Immune Response, 79-7114

Sarcoma, Osteogenic
 Abdominal Neoplasms
 Azobenzene, 79-6766
 Aflatoxin B1
 Carcinogenic Activity, Monkey
 79-6790
 Cell Differentiation
 Ultrastructural Study, 79-7115
 Genetics
 Case Report, 79-7116
 Multiple Myeloma
 Drug Therapy, 79-6908
 Radiation, Ionizing, 79-6908
 Radiation, Ionizing
 Case Report, 79-6908
 Strontium
 Virus, FBR Murine Sarcoma, 79-6975
 Transplantation, Heterologous
 Bone Induction, 79-7117
 Virus, FBR Murine Sarcoma
 Isolation and Characterization
 79-6975

Sarcoma, Reticulum Cell
 Epidemiology
 Saudi Arabia, 79-7146
 2-Imidazolidinethione, *N*-Nitroso-
 Dose-Response Study, 79-6736
 Leukemia, Myeloblastic
 Epidemiology, 79-7105
 B-Lymphocytes
 Case Report, Child, 79-7112
 Solvents
 Air Pollution, 79-7165
 Theca Cell Tumor
 Virus Activation, 79-7010
 Thymus Gland
 Transplantation, 79-7112
 Virus, Murine Leukemia
 Autoantibodies, 79-7097

Sarcoma, Yoshida
 Macrophages
 Growth, 79-7081

Scleroderma
 Breast Neoplasms
 Epidemiology, 79-7158
 Leukemia
 Lymphoma, 79-7158
 Lymphoma
 Epidemiology, 79-7158
 Uterine Neoplasms
 Sex Factors, 79-7158

Sebaceous Gland Neoplasms
 Carcinoma
 1,1'-Biphenyl, 4,4'-Diisocyanato-
 3,3'-dimethoxy-, 79-6769

Selenium
 Liver Neoplasms
 Acetamide, *N*-Fluoren-2-yl-, 79-6685

Serine, Diazoacetate (Ester)
 Choline
 Glutamyltranspeptidase, 79-6683
 Liver Neoplasms
 Acetamide, *N*-Fluoren-2-yl-, 79-6683
 Choline, 79-6683
 Precancerous Conditions, 79-6683

Sertoli Cell Tumor
 Anthraquinone, 1-Amino-2-methyl-
 Dose-Response Study, 79-6792
 Kidney Neoplasms
 Adenocarcinoma, 79-6792

Serum Albumin
 Sarcoma
 Benzo(a)pyrene, 79-6839

Sex Chromosomes
 3-Heptanone, 6-(Dimethylamino)-4,4-
 diphenyl-, Hydrochloride
 Mutagenic Activity, Mouse, 79-6671

Sialyltransferase
 Mammary Neoplasms, Experimental
 Adenocarcinoma, 79-6817

Skin Diseases
 Ethylene, Chloro-
 Histopathological Study, 79-6663
 Occupational Hazard, 79-6663
 Radiation, Ionizing
 Radiation Injuries, 79-6910

Skin Neoplasms
 Adenofibroma
 Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-
 79-6713

Angioma
 Ultraviolet Rays, 79-6885

Angiosarcoma
 Ultraviolet Rays, 79-6885

Arsenic
 Water Pollution, 79-6644
 Benz(a)anthracene, 7,12-Dimethyl-
 Aroclor 1254, 79-6813
 Azobenzene, 3,3',4,4'-Tetrachloro-
 79-6813

Benzo(e)pyrene, 79-6815
 Dibenzo-*p*-dioxin, 2,7-Dichloro-
 79-6813
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 79-6813
 Fluoranthene, 79-6815
 Mezerin, 79-6800
 Pyrene, 79-6815
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6800, 79-6813

Benzo(a)pyrene
 Benzo(e)pyrene, 79-6815
 Carbamic Acid, Ethylnitroso-, Ethyl Es-
 ter
 Histological Study, Rat, 79-6701
 Carcinoma, Basal Cell
 Arsenic, 79-6644
 Carcinoma, Epidermoid
 Arsenic, 79-6644

Skin Neoplasms (cont'd)
 1,1'-Biphenyl, 4,4'-Diisocyanato-
 3,3'-dimethoxy-, 79-6769
 Carcinoma, Basal Cell, 79-7168
 Saudi Arabia, 79-7146
 Ultraviolet Rays, 79-6885, 79-6889
 79-7168
 Carcinoma In Situ
 Ultraviolet Rays, 79-6889
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 Antineoplastic Activity, 79-6813
 DNA Repair
 Fibroblasts, 79-6875
 Epidermodysplasia Verruciformis
 Case Report, 79-7030
 Ethylene, 1,1-Dichloro-
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6666
 Hyperplasia
 Ornithine Decarboxylase, 79-6800
 Papilloma
 Propene, 1,3-Dichloro-, 79-6666
 Propane, 1,2-Dibromo-3-chloro-
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6666
 Propene, 3-Chloro-
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6666
 Ultraviolet Rays
 Antioxidants, 79-6888
 Caffeine, 79-6876
 Diet, 79-6888
 Dose-Response Study, 79-6884
 Dose-Response Study, Review
 79-6627
 Epidemiology, 79-7168
 Epidemiology, Review, 79-6625
 79-6627, 79-6642
 Histopathological Study, 79-6885
 Immunity, Cellular, 79-6887
 Psoralen, 8-Methoxy-, 79-6872
 Quinoline, 7-Chloro-
 4-((4-(diethylamino)-1-
 methylbutyl)amino)-, 79-6876
 Retinoic Acid, 79-6889
 Solar Simulators, 79-6881
 Temperature, Humidity, 79-6886
 12-*O*-Tetradecanoylphorbol-13-acetate
 79-6872
 Theophylline, 79-6876
 Transplantation Immunology, 79-6887
 Virus, Herpes Simplex
 Co-carcinogenic Effect, Review
 79-6641
 Virus, Papilloma
 Genetics, 79-7030

Smoking
 Bladder Neoplasms
 Carcinoma, Transitional Cell, 79-7132
 Carcinoma, Epidermoid
 Age Factors, 79-7138
 Laryngeal Neoplasms
 Animal Model, Hamster, 79-6822
 Epidemiology, 79-7181
 Precancerous Conditions, 79-6845
 Retinol Palmitate, 79-6845
 Lung Neoplasms
 Asbestosis, 79-6650
 Sex Factors, 79-7138
 Virus, Influenza, 79-6633
 Mouth Neoplasms
 Carcinoma, Epidermoid, 79-6640
 Nasopharyngeal Neoplasms
 Co-carcinogenic Effect, 79-7141
 Neoplasms
 Co-carcinogenic Effect, 79-7177
 Nose Neoplasms
 Precancerous Conditions, 79-6838
 Respiratory Tract Neoplasms
 Animal Model, Hamster, Review
 79-6611
 Rhinitis
 Histological Study, Hamster, 79-6838

Sodium Azide
Tradescantia paludosa

Sodium Azide (cont'd)
Mutagenic Activity, 79-6899

Solvents

2-Butanone
Epidemiology, 79-7165
Hodgkin's Disease
Air Pollution, 79-7165
Laryngeal Neoplasms
Air Pollution, 79-7165
Leukemia
Air Pollution, 79-7165
Pancreatic Neoplasms
Air Pollution, 79-7165
Sarcoma, Reticulum Cell
Air Pollution, 79-7165

Somatotropin

Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-
79-6811

Spermatozoa

3-Heptanone, 6-(Dimethylamino)-4,4-
diphenyl-, Hydrochloride
Chromosome Aberrations, 79-6671

Spinal Cord Neoplasms

Meningioma
Karyotyping, 79-7099

Splenic Neoplasms

Angiosarcoma
Phosphamidin, 79-6655
Hemangioma
Phosphamidin, 79-6655
Hemangiopericytoma
Azobenzene, 79-6766
Radiation, Ionizing
Hamster, 79-6915
Virus-Like Particles, 79-6915
Sarcoma
 α -Toluidine, Hydrochloride, 79-6752
Virus, SV40, 79-7041

Squalene

Adenocarcinoma
Cholesterol, 79-7197

Stannane, Diacetoxydibutyl-

Hepatosarcoma
Dose-Response Study, 79-6775
Uterine Neoplasms
Carcinogenic Potential, 79-6775

4-Stilbenamine, N,N-Dimethyl-

Acetamide, N-(4-(1,2-Dihydroxy-2-
phenylethyl)phenyl)-
RNA Adducts, 79-6848
RNA Adducts
Liver, Rat, 79-6848

4,4'-Stilbenediol, α,α' -Diethyl-

Abnormalities
Vagina, Cervix, 79-7174
Acetamide, N-Fluoren-2-yl-
Ames Test, 79-6679
Acetohydroxamic Acid, N-Fluoren-2-yl-
Ames Test, 79-6679
Benz(a)anthracene, 7,12-Dimethyl-
Co-carcinogenic Effect, 79-6850
Bladder Neoplasms
1-Butanol, 4-(Butylnitrosamino)-
79-6849
Breast Neoplasms
Metabolism, 79-6851
Co-carcinogenic Effect
Transplacental Exposure, 79-6850
Cysts
Testis, Mouse, 79-6846
Estradiol
Antigens, 79-6852
Glucuronates
Biliary, Urinary Metabolites, 79-6851
Gynecologic Neoplasms
Carcinoma, 79-7174
Co-carcinogenic Effect, 79-6850
Precancerous Conditions, 79-6852
Transplacental Carcinogenesis
79-6703, 79-6846

4,4'-Stilbenediol, α,α' -Diethyl- (cont'd)

Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6847
Adenofibroma, 79-6847
Co-carcinogenic Effect, 79-6850
Melanoma
Co-carcinogenic Effect, 79-6850
Metaplasia
Prostate, Mouse, 79-6846
Nervous System Neoplasms
Neurilemmoma, 79-6703
Perinatal Carcinogenesis
Species Difference, Review, 79-6602
Pituitary Neoplasms
Carcinogenic Activity, Rat, 79-6847
Propiophenone, *p*-Hydroxy-
Biliary, Urinary Metabolites, 79-6851
Radiation, Ionizing
Co-carcinogenic Effect, 79-6847
Sterility
Transplacental Effects, 79-6846
Stomach Neoplasms
Co-carcinogenic Effect, 79-6850
Testicular Neoplasms
Transplacental Carcinogenesis
79-6703
Transplacental Carcinogenesis
Bioassays, Review, 79-6620
Mouse, Rat, Review, 79-6619
Virus, Cytomegalo
Virus Replication, 79-7011
Virus, Herpes Simplex
Cell Transformation, Neoplastic
79-7011
Thymidine Kinase, 79-7011

Stomach Neoplasms

Adenocarcinoma
Gastrectomy, 79-7129
Guanidine, 1-Methyl-3-nitro-1-nitroso-
79-6866
NADH, NADPH Oxidoreductases
79-7128
Neoplasm Transplantation, 79-6866
Carbon Tetrabromide
Carcinogenic Activity, Mouse, 79-6666
Carcinoma
Gastrectomy, 79-7129
Carcinoma, Epidermoid
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-
furyl)-, 79-6690
Benzenamine, N-Hydroxy-N-nitroso-,
Ammonium Salt, 79-6754
Carbamic Acid, Diethyldithio-, 2-
Chloroallyl Ester, 79-6702
Propene, 3-Chloro-, 79-6669
Carcinoma, Mucinous
NADH, NADPH Oxidoreductases
79-7128
Cell Differentiation
Prognosis, 79-7128
Ethane, 1,2-Dibromo-
Carcinogenic Activity, Mouse, 79-6666
Ethnic Groups
Epidemiology, Israel, 79-7183
Gastrectomy
Bile Reflux, 79-7170
Epidemiology, 79-7170
Guanidine, 1-Methyl-3-nitro-1-nitroso-
79-7129
Precancerous Conditions, 79-7129
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Cells, Cultured, 79-6866
Neoplasms, Multiple Primary
Benz(a)anthracene, 7,12-Dimethyl-
79-6850
Nutrition
Epidemiology, Israel, 79-7183
Papilloma
Propene, 3-Chloro-, 79-6669
Propane, 1,2-Dibromo-3-chloro-
Carcinogenic Activity, Mouse, 79-6666
Propene, 1-Chloro-
Carcinogenic Activity, Mouse, 79-6666
Propene, 3-Chloro-
Carcinogenic Potential, 79-6669
Propene, 1,3-Dichloro-

Stomach Neoplasms (cont'd)

Carcinogenic Activity, Mouse, 79-6666
4,4'-Stilbenediol, α,α' -Diethyl-
Co-carcinogenic Effect, 79-6850

Streptococcus faecalis

Liver Neoplasms
Mouse, 79-6643

Strontium

Sarcoma, Osteogenic
Virus, FBR Murine Sarcoma, 79-6975

Sulfallate

see Carbamic Acid, Diethyldithio-, 2-
Chloroallyl Ester

3-Sulfolene

see Thiophene, 2,5-Dihydro-, 1,1-
Dioxide

Surgery, Operative

Colonic Neoplasms
Adenocarcinoma, 79-6919

Tannic Acid

DNA Replication
Inhibitory Factor, 79-6786
Lymphocytes, 79-6786
L Cells
DNA Replication, 79-6786
Mammary Neoplasms, Experimental
DNA Replication, 79-6786
Respiratory Tract Neoplasms
Carcinogenic Potential, 79-6786

Telangiectasis

Leukemia, Lymphoblastic
Chromosome Abnormalities, 79-7109

Telocidin B, Dihydro

Erythroleukemia
Cell Differentiation, 79-6844
Leukemia, Myelocytic
Cell Adhesion, 79-6844
13-*cis*-Retinoic Acid
Ornithine Decarboxylase, 79-6844

Tellurium, Tetrakis(diethyldithiocar-

bamate)-
Eye Neoplasms
Adenoma, 79-6658
Mesothelioma
Carcinogenic Potential, 79-6658

Teratoid Tumor

Histocompatibility Antigens
Chromosomes, 79-7079
Graft Rejection, 79-7079
Kidney Neoplasms
Urea, Ethyl Nitroso-, 79-6715
Testicular Neoplasms
Histocompatibility Antigens, 79-7098

Terephthalic Acid, Dimethyl Ester

Hepatosarcoma
Carcinogenic Potential, 79-6749
Lung Neoplasms
Adenoma, 79-6749
Lymphoma
Carcinogenic Potential, 79-6749

Testicular Neoplasms

Disgerminoma
Histocompatibility Antigens, 79-7098
Leydig Cell Tumor
Estradiol, 79-7137
Fenthion, 79-6654
Prolactin, 79-7137
4,4'-Stilbenediol, α,α' -Diethyl-
Transplacental Carcinogenesis
79-6703

Teratoid Tumor

Histocompatibility Antigens, 79-7098

Testosterone

Bladder Neoplasms
1-Butanol, 4-(Butylnitrosamino)-
79-6849

Testosterone, Propionate

Vaginal Neoplasms

Testosterone, Propionate (cont'd)
Estradiol, 79-6853
Precancerous Conditions, 79-6853

12-*O*-Tetradecanoylphorbol-13-acetate
Actin
Fibroblasts, 79-6797
RNA Replication, 79-6797
Cell Differentiation
Bone Marrow, 79-6794
Clostridiopeptidase A
Cell Division, 79-6795
Fibroblasts, 79-6795
DNA Replication
Cells, Cultured, 79-6793
Growth Substances
Granulocytes, 79-6794
Macrophages, 79-6794
Isoproterenol
Adenosine Cyclic 3',5' Monophosphate, 79-6800
Leukemia, Myelocytic
Cell Differentiation, 79-6794, 79-6796
Phagocytosis, 79-6794
Lipopolysaccharides
Cell Differentiation, 79-6796
Ornithine Decarboxylase
Cells, Cultured, 79-6793
Enzyme Induction, 79-6800
Papilloma
Cholanthrene, 3,11-Dimethyl-, 79-6827
Cholanthrene, 3-Methyl-, 79-6827
Peptides
Binding, 79-6799, 79-6809
Fibroblasts, 79-6799
Prostaglandins E
Benzoic Acid, 2-(Acetyloxy)-, 79-6795
Epidermis, Mouse, 79-6798
Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-, 79-6795
Prostaglandins F
Epidermis, Mouse, 79-6798
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 79-6800, 79-6813
Ethylene, 1,1-Dichloro-, 79-6666
Propane, 1,2-Dibromo-3-chloro-, 79-6666
Propene, 3-Chloro-, 79-6666
Ultraviolet Rays, 79-6872
Ultraviolet Rays
Cell Transformation, Neoplastic, 79-6883
Virus, Adeno 5
Cell Transformation, Neoplastic, 79-6801
Virus, Epstein-Barr
DNA Replication, 79-7017
Virus, Rous Sarcoma
Cell Transformation, Neoplastic, 79-6950

Theca Cell Tumor
Ovarian Neoplasms
Virus, Cytomegalo, 79-7010
Sarcoma, Reticulum Cell
Virus Activation, 79-7010
Virus, Cytomegalo
Case Report, 79-7010

Theophylline
Skin Neoplasms
Ultraviolet Rays, 79-6876

Thiophene, 2,5-Dihydro-, 1,1-Dioxide
Hepatoma
Dose-Response Study, 79-6778

Thorium Dioxide
Anemia, Aplastic
Case Report, 79-6770
Hemangioendothelioma
Case Report, 79-6770
Liver Neoplasms
Hemangioendothelioma, 79-6770

Thrombopenia
Ethylene, Chloro-

Thrombopenia (cont'd)
Occupational Hazard, 79-6663

Thymidine Kinase
Virus, Herpes Simplex
4,4'-Stilbenediol, α, α' -Diethyl-, 79-7011

Thymus Gland
Immunoblastic Lymphadenopathy
Transplantation, 79-7112
Sarcoma, Reticulum Cell
Transplantation, 79-7112

Thyroid Neoplasms
Adenocarcinoma
Carbamic Acid, Diethyldithio-, 2-Chloroallyl Ester, 79-6702
Radiation, Ionizing, 79-7140
Urea, 1,1,3-Trimethyl-2-thio-, 79-6711
Adenoma
1,5-Naphthalenediamine, 79-6772
Phosphamidon, 79-6655
Carcinoma
Phosphamidon, 79-6655
Radiation, Ionizing, 79-7166
Carcinoma, Papillary
1,5-Naphthalenediamine, 79-6772
Radiation, Ionizing, 79-6901
Cyanamide, Calcium Salt
Precancerous Conditions, 79-6647
Cystadenoma, Papillary
1,5-Naphthalenediamine, 79-6772
Guthion
Carcinogenic Potential, 79-6777
Hodgkin's Disease
Radiotherapy, 79-7166
Phosphamidon
Carcinogenic Potential, 79-6655
Radiation, Ionizing
Epidemiology, 79-7140
Urea, 1-(Hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolylsulfonyl)-
Carcinogenic Potential, 79-6719
Tolazamide, 79-6719
Urea, 1,1,3-Trimethyl-2-thio-
Dose-Response Study, 79-6711

Thyroiditis, Lymphomatous
Lung Neoplasms
Epidemiology, Japan, 79-7139

Thyrotropin
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 79-6811

Thyrotropin Releasing Hormone
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 79-6811

***p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-**
Ear Neoplasms
Carcinoma, Epidermoid, 79-6750
Leukemia
Carcinogenic Potential, 79-6750
Lung Neoplasms
Adenoma, 79-6750
Lymphoma
Carcinogenic Potential, 79-6750
Mammary Neoplasms, Experimental
Adenocarcinoma, 79-6750
Nose Neoplasms
Neuroblastoma, 79-6750
Uterine Neoplasms
Adenocarcinoma, 79-6750

Toluene
Benzo(rst)pentaphene
Emission Spectra, 79-6761

Toluene, α -Chloro-
Nucleosides
Alkylation, 79-6740

***o*-Toluidine, 5-Chloro-**
Adrenal Gland Neoplasms
Pheochromocytoma, 79-6751

***o*-Toluidine, 5-Chloro-** (cont'd)
Angiosarcoma
Dose-Response Study, 79-6751
Hepatoma
Dose-Response Study, 79-6751
Pheochromocytoma
Dose-Response Study, 79-6751

***o*-Toluidine, Hydrochloride**
Fibroma
Carcinogenic Potential, 79-6752
Mesothelioma
Carcinogenic Potential, 79-6752
Splenic Neoplasms
Sarcoma, 79-6752
Urogenital Neoplasms
Carcinoma, Transitional Cell, 79-6752
Mesothelioma, 79-6752

Tosyllysine Chloromethyl Ketone
Virus, Avian Sarcoma
Cell Transformation, Neoplastic, 79-6933
Phosphotransferases, ATP, 79-6933

Tracheal Neoplasms
Adenocarcinoma
Precancerous Conditions, 79-6710
Urea, Methyl Nitroso-, 79-6708
Benz(a)anthracene, 7,12-Dimethyl-, 79-6802
Neoplasm Regression, Spontaneous, 79-6814
Precancerous Conditions, 79-6802
79-6814
Carcinoma
Cholanthrene, 3-Methyl-, 79-6824
79-6825
Fibrosarcoma, 79-6824, 79-6825
Precancerous Conditions, 79-6710
Urea, Methyl Nitroso-, 79-6710
Carcinoma, Epidermoid
Benz(a)anthracene, 7,12-Dimethyl-, 79-6802, 79-6814
Diethylamine, *N*-Nitroso-, 79-6725
Precancerous Conditions, 79-6710
Urea, Methyl Nitroso-, 79-6708
Carcinoma In Situ
Benz(a)anthracene, 7,12-Dimethyl-, 79-6814
Cell Differentiation
Endoplasmic Reticulum, 79-6725
Cholanthrene, 3-Methyl-, 79-6824, 79-6825
Asbestos, 79-6824, 79-6825
Iron Oxide, 79-6824, 79-6825
Diethylamine, *N*-Nitroso-
Transplacental Carcinogenesis, 79-6725
Fibrosarcoma
Cholanthrene, 3-Methyl-, 79-6824
79-6825
Papilloma
Diethylamine, *N*-Nitroso-, 79-6725
Polyps
Diethylamine, *N*-Nitroso-, 79-6725
Urea, Methyl Nitroso-
Animal Model, Hamster, 79-6708
Dose-Response Study, Hamster, 79-6710

Tradescantia paludosa
Hydrazoic Acid
Mutagenic Activity, 79-6899
Methanesulfonic Acid, Ethyl Ester
Mutagenic Activity, 79-6899
Radiation, Ionizing
Mutagenic Activity, 79-6899
Sodium Azide
Mutagenic Activity, 79-6899

Transferrin
Breast Neoplasms
Prostaglandins F, 79-7200
Cell Transformation, Neoplastic
Cell Cycle Kinetics, 79-7187

Transformation, Genetic
Virus, C-Type RNA Tumor
Carcinogenic Potential, Review

Transformation, Genetic (cont'd)
 Carcinogenic Potential, Review
 79-6635
 Virus, Harvey Murine Sarcoma-Leukemia
 DNA, Viral, 79-6982
 Virus, Rous Sarcoma
 Virus Replication, 79-6946

Transplantation
 Immunoblastic Lymphadenopathy
 Thymus Gland, 79-7112
 Sarcoma, Reticulum Cell
 Thymus Gland, 79-7112

Transplantation, Heterologous
 Mesenchymoma
 Leukemia, Myelocytic, 79-7118
 Sarcoma, Osteogenic
 Bone Induction, 79-7117

Transplantation, Homologous
 Adenocarcinoma
 Neoplasm Metastasis, 79-6728
 Eye Neoplasms
 Light, 79-6894
 Graft vs Host Reaction
 Phagocytes, 79-7089
 Melanoma
 Graft vs Host Reaction, 79-7089
 Immunity, Cellular, 79-7089
 Pancreatic Neoplasms
 Dipropylamine, 2,2'-Dioxo-N-nitroso-
 79-6728

Transplantation Immunology
 Fibrosarcoma
 Radiation, Ionizing, 79-6907
 Ultraviolet Rays, 79-6887
 Leukemia
 Antigens, Neoplasm, 79-6878
 Histocompatibility Antigens, 79-6878
 Leukemia, Myelocytic
 Killer Cells, 79-7075
 Lymphoma
 Hybrid Cells, 79-7071
 Killer Cells, 79-7075
 Mammary Neoplasms, Experimental
 Hybrid Cells, 79-7071
 Skin Neoplasms
 Ultraviolet Rays, 79-6887
 Ultraviolet Rays
 Antigens, Neoplasm, 79-6879
 Virus, Adeno 12
 Antigens, Viral, 79-7049
 Histocompatibility Antigens, 79-7049
 Virus, SV40
 Histocompatibility Antigens, 79-7040

Trauma
 see Wounds and Injuries

Triazene, 3,3-Dimethyl-1-phenyl-
 Guanine, 7-Methyl-
 Perinatal Carcinogenesis, 79-6709
 Purine, 2-Amino-6-methoxy-
 Perinatal Carcinogenesis, 79-6709

Tubulin
 RNA, Messenger
 Poly A, 79-7191

Tumor Phylloides
 see Cystosarcoma Phylloides

Tunicamycin
 Virus, Rous Sarcoma
 Viral Proteins, 79-6941

Turpentine
 Carcinoma 256, Walker
 Wounds and Injuries, 79-6657

Tyrosinase
 Melanoma
 MSH, 79-7194
 MSH
 Actinomycin D, 79-7194
 Cycloheximide, 79-7194

Ultrasonics
 Chromatids

Ultrasonics (cont'd)
 Lymphocytes, 79-6925
 Metaphase, 79-6925

Ultraviolet Rays
 Acetamide, N-(Acetyloxy)-N-fluoren-2-yl-
 Cell Transformation, Neoplastic
 79-6891
 Anemia, Aplastic
 DNA Repair, 79-6890
 Angiosarcoma
 Dose-Response Study, 79-6882
 Antigens, Neoplasm
 Transplantation Immunology, 79-6879
 Benz(a)anthracene, 7,12-Dimethyl-
 Cell Survival, 79-6871
 DNA Replication, 79-6871
 Caffeine
 DNA Repair, 79-6876
 Carcinogen, Chemical
 Co-carcinogenic Effect, Review
 79-6624
 Carcinogen, Environmental
 Photochemistry, Review, 79-6624
 Carcinoma, Epidermoid
 Dose-Response Study, 79-6882
 Cell Transformation, Neoplastic
 Dose-Response Study, 79-6883
 Cholanthrene, 3-Methyl-
 Cell Transformation, Neoplastic
 79-6883
 Cholesterol
 Carcinogenic Activity, 79-6888
 DNA Photolysis
 Cell Transformation, Neoplastic
 79-6874
 DNA Repair, 79-6874
 DNA Repair
 Azaguanine, Thioguanine Resistance
 79-6877
 Cell Transformation, Neoplastic, Review,
 79-6626
 Chloramphenicol, 79-6622
 Culture Media, 79-6870
 Fibroblasts, 79-6873, 79-6877, 79-6890
 Mutagenic Activity, Review, 79-6625
 Mutagenic, Carcinogenic Activity, Review,
 79-6622, 79-6623
 Nucleotides, 79-6873
 Peptide Hydrolases, Review, 79-6623
 DNA Replication
 Cell Cycle Kinetics, 79-6870
 Contact Inhibition, 79-6870
 Erythema
 Carcinogenic Potential, 79-6882
 Fibrosarcoma
 Dose-Response Study, 79-6882
 Transplantation Immunology, 79-6887
 Fluorescence Light
 Mutagenic, Toxic Effects, 79-6880
 HeLa Cells
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6871
 Cell Survival, 79-6871
 Leukemia
 Immune Response, Mouse, 79-6878
 Lymphocyte Culture Test, Mixed
 79-7070
 Lymphocytes
 Suppressor Cells, 79-6879
 Lymphoma
 Mutagenic, Toxic Effects, 79-6880
 Mammary Neoplasms, Experimental
 Immune Response, Mouse, 79-6878
 Melanoma
 Co-carcinogenic Effect, Review
 79-6625, 79-6628
 Epidemiology, Review, 79-6628
 Pigmentation, 79-7148
 Mutagenic Activity
 Mathematical Model, 79-6869
 Polysulfone
 Dosimeters, 79-6892
 Psoralen, 8-Methoxy-
 DNA Cross-Links, 79-6872
 Radiation Effects

Ultraviolet Rays (cont'd)
 Action Spectrum, 79-6621
 Skin, Review, 79-6621
 Radiation, Ionizing
 Co-carcinogenic Effect, 79-6891
Saccharomyces cerevisiae
 Mutagenic Activity, 79-6869
 Sarcoma
 Immune Response, Mouse, 79-6878
 Skin Neoplasms
 Antioxidants, 79-6888
 Caffeine, 79-6876
 Carcinoma, Epidermoid, 79-6889
 79-7168
 Carcinoma In Situ, 79-6889
 Diet, 79-6888
 Dose-Response Study, 79-6884
 Dose-Response Study, Review
 79-6627
 Epidemiology, 79-7168
 Epidemiology, Review, 79-6625
 79-6627, 79-6642
 Immunity, Cellular, 79-6887
 Psoralen, 8-Methoxy-, 79-6872
 Quinoline, 7-Chloro-
 4-((4-(diethylamino)-1-methylbutylamino)-, 79-6876
 Retinoic Acid, 79-6889
 Solar Simulators, 79-6881
 Temperature, Humidity, 79-6886
 12-O-Tetradecanoylphorbol-13-acetate
 79-6872
 Theophylline, 79-6876
 Transplantation Immunology, 79-6887
 Spectrum Analysis
 Solar Simulators, 79-6881
 12-O-Tetradecanoylphorbol-13-acetate
 Cell Transformation, Neoplastic
 79-6883
 Virus, C-Type RNA Tumor
 Antipain, 79-6893
 Virus Activation, 79-6893
 Weather
 Radiation Injuries, 79-6886
 Xeroderma Pigmentosum
 DNA Repair, 79-6629, 79-6873
 79-6875, 79-6877, 79-6890

Uracil, 5-Fluoro-
 Carcinoma, Basal Cell
 Neoplasm Recurrence, Local, 79-6738
 Carcinoma, Epidermoid
 Case Report, 79-6738

Urea, 1-((p-Acetylphenyl)sulfonyl)-3-cyclohexyl-
 Leukemia
 Dose-Response Study, 79-6720
 Lymphoma
 Dose-Response Study, 79-6720

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Leukemia
 Epidemiology, 79-7155

Urea, 1-Butyl-1-nitroso-
 Nervous System Neoplasms
 Transplacental Carcinogenesis, Review
 79-6607

Urea, 3-(p-Chlorophenyl)-1-methyl-1-nitroso-
 Structure-Activity Relationship
 Mutagenic Activity, 79-6867

Urea, 1,3-Dimethyl-1-nitroso-
 Ames Test
 Aryl Derivatives, 79-6867

Urea, Ethyl-
 Nervous System Neoplasms
 Nitrous Acid, Sodium Salt, 79-6703

Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-
 Hepatoma
 Dose-Response Study, 79-6713
 Mammary Neoplasms, Experimental
 Adenofibroma, 79-6713
 Cystadenoma, 79-6713

- Urea, 1-Ethyl-3-(5-nitro-2-thiazolyl)-**
(cont'd)
Skin Neoplasms
Adenofibroma, 79-6713
- Urea, Ethyl Nitroso-**
Brain Neoplasms
Ganglioneuroma, 79-6715
Cell Differentiation
Carcinogenic Activity, Opossum
79-6715
Ependyoma
Mercury, Chloromethyl-, 79-6651
Erythrocybus patas
Maternal-Fetal Exchange, 79-6716
Eye Neoplasms
Neuroepithelioma, 79-6715
Glioma
Transplacental Carcinogenesis, Review
79-6607, 79-6608
Jaw Neoplasms
Ameloblastoma, 79-6715
Kidney Neoplasms
Nephroblastoma, 79-6715
Teratoid Tumor, 79-6715
Lung Neoplasms
Adenoma, 79-6714
Amniotic Fluid Injection, 79-6714
Transplacental Carcinogenesis, Review
79-6608
Lymphosarcoma
Carcinogenic Activity, Mouse, 79-6712
Maternal-Fetal Exchange
Animal Model, Mouse, 79-6714
Mercury, Chloromethyl-
Transplacental Carcinogenesis
79-6651
Nervous System Neoplasms
Gynecologic Neoplasms, 79-6703
Transplacental Carcinogenesis
79-6703
Neurilemmoma
Mercury, Chloromethyl-, 79-6651
Neurofibroma
Transplacental Carcinogenesis, Review
79-6607
Odontogenic Tumor
Carcinogenic Activity, Opossum
79-6715
Perinatal Carcinogenesis
Mouse, Review, 79-6609
Structure-Activity Relationship
Nucleic Acids, Binding, 79-6707
Tissue Distribution
Transplacental Effect, 79-6716
Transplacental Carcinogenesis
Genetics, Review, 79-6618
- Urea, 1,1'-Ethylenebis(1-nitroso)-**
Cysteine
Polylysine, Binding, 79-6707
Structure-Activity Relationship
Nucleic Acids, Binding, 79-6707
- Urea, 1-(Hexahydro-1H-azepin-1-yl)-3-(p-tolylsulfonyl)-**
Thyroid Neoplasms
Carcinogenic Potential, 79-6719
Tolazamide
Thyroid Neoplasms, 79-6719
- Urea, 1-(2-Hydroxyethyl)-1-nitroso-**
Lymphosarcoma
Carcinogenic Activity, Mouse, 79-6712
- Urea, 3-(p-Methoxyphenyl)-1-methyl-1-nitroso-**
Structure-Activity Relationship
Mutagenic Activity, 79-6867
- Urea, Methyl Nitroso-**
Ames Test
Aryl Derivatives, 79-6867
Cysteine
Polylysine, Binding, 79-6707
Deoxyribonucleosides
DNA Replication, 79-6705
DNA Repair
Brain, Liver, 79-6709
- Urea, Methyl Nitroso-**(cont'd)
Liver, Rat, 79-6705
Guanine, 7-Methyl-
Neurons, 79-6704
Perinatal Carcinogenesis, 79-6709
Lymphosarcoma
Virus, Feline Leukemia, 79-6999
Methylation
Brain, Rat, 79-6704
Mutagenic Activity
Thioguanine Resistance, 79-6700
Nervous System Neoplasms
Transplacental Carcinogenesis, Review
79-6607
Purine, 2-Amino-6-methoxy-
Neurons, 79-6704
Perinatal Carcinogenesis, 79-6709
Structure-Activity Relationship
Nucleic Acids, Binding, 79-6707
Tracheal Neoplasms
Adenocarcinoma, 79-6708
Animal Model, Hamster, 79-6708
Carcinoma, 79-6710
Carcinoma, Epidermoid, 79-6708
Dose-Response Study, Hamster
79-6710
Transplacental Carcinogenesis
Genetics, Review, 79-6618
Virus, Feline Leukemia
Immune Response, 79-6999
- Urea, 1-Methyl-1-nitroso-3-phenyl-**
Structure-Activity Relationship
Mutagenic Activity, 79-6867
- Urea, N-Nitroso-N-propyl-**
Nervous System Neoplasms
Transplacental Carcinogenesis, Review
79-6607
Structure-Activity Relationship
Nucleic Acids, Binding, 79-6707
- Urea, 1-Phenyl-2-thio-**
Dose-Response Study
Carcinogenic Potential, 79-6718
- Urea, 1,1,3-Trimethyl-2-thio-**
Thyroid Neoplasms
Adenocarcinoma, 79-6711
Dose-Response Study, 79-6711
- Uridine, 5-Bromo-2'-deoxy-**
Virus, C-Type RNA Tumor
Antipain, 79-6893
- Urine**
Ethanol, N-Nitrosoiminodi-
Adsorption, Skin, 79-6696
- Urogenital Neoplasms**
Blood Coagulation Disorders
Epidemiology, 79-7172
Carcinoma, Transitional Cell
o-Toluidine, Hydrochloride, 79-6752
Mesothelioma
o-Toluidine, Hydrochloride, 79-6752
- Urologic Neoplasms**
p-Acetophenetidine
Nephritis, Interstitial, 79-6615
p-Benzoquinone Dioxime
Dose-Response Study, 79-6763
Carcinogen, Environmental
Nephritis, Interstitial, 79-6615
2-Naphthylamine
Animal Model, Hamster, 79-6822
Nephritis, Interstitial
Precancerous Conditions, Review
79-6615
- Uterine Neoplasms**
Adenocarcinoma
Enovid, 79-6854
Estrogens, 79-7173
Histological Study, 79-7171
Pregn-4-ene-3,20-dione, 17-(Acetyloxy)-
6 α -methyl-, 79-6854
p-Tolamide, N-Isopropyl- α -(2-methylhydrazino)-, 79-6750
Carcinoma
- Uterine Neoplasms**(cont'd)
Histological Study, 79-7171
Carcinoma, Epidermoid
Histological Study, 79-7171
Endometrial Hyperplasia
Progestational Hormones, 79-7173
Epidemiology
Greenland, 79-7151
Estrogens
Epidemiology, 79-7171, 79-7173
Hair Dyes
Epidemiology, 79-7156
Polyps
1,1'-Biphenyl, 4,4'-Diisocyanato-
3,3'-dimethoxy-, 79-6769
Progestational Hormones
Epidemiology, 79-7173
Sarcoma
Benzenediazosulfonic Acid, *p*-(Dime-
thylamino)-, Sodium Salt, 79-6656
Scleroderma
Sex Factors, 79-7158
Stannane, Diacetoxydibutyl-
Carcinogenic Potential, 79-6775
- Vaginal Neoplasms**
5 α -Androstan-3-one, 17 β -Hydroxy-
Precancerous Conditions, 79-6853
Estradiol
Precancerous Conditions, 79-6853
Hyperplasia
Estradiol, 79-6853
Testosterone, Propionate
Estradiol, 79-6853
Precancerous Conditions, 79-6853
- Valeric Acid, 2,2-Diphenyl-, 2-(Die-
thylamino)ethyl Ester, HCl**
Aryl Hydrocarbon Hydroxylases
Lymphocytes, 79-6819
- Vinylamine, N-Ethyl-N-nitroso-**
Digestive System Neoplasms
Hamster, Review, 79-6610
Respiratory Tract Neoplasms
Hamster, Review, 79-6610
- Viral Proteins**
Leukemia, Radiation-Induced
Mutation, Mouse, 79-6903
Radiation, Ionizing, 79-6903
Plasmacytoma
Virus, C-Type RNA Tumor, 79-6993
Virus, Avian Leukosis
Virus, Recombinant, 79-6927
Virus, Avian Myelocytomatosis
Cell Transformation, Neoplastic
79-6931
Isolation and Characterization
79-6931
Virus, Avian Sarcoma
Cell Membrane, 79-6932
Cell Transformation, Neoplastic
79-6932
Virus, Gazdar Murine Sarcoma
A-Type Particles, 79-6979
Immunoprecipitation, 79-6979
Virus, Herpes Simplex 2
Antigen-Antibody Reactions, 79-7009
Isolation and Characterization
79-7009
Virus, Murine C-Type Myeloma
Isolation and Characterization
79-6993
Virus, Murine Leukemia
Antibody Specificity, 79-6957
Host Range, 79-6958
Radioimmunoassay, 79-6958
Virus, Murine Mammary Tumor
Antigenic Determinants, 79-6964
Virus, Polyoma
Binding Sites, 79-7025
Virus, Rauscher Murine Leukemia
Antigenic Determinants, 79-6990
Histocompatibility Antigens, 79-6991
Virus, Rous-Associated
Antigenic Determinants, 79-6948
Virus, Rous Sarcoma

- Viral Proteins (cont'd)**
Antigenic Determinants, 79-6941
Glucose, 2-Deoxy-, 79-6941
Tunicamycin, 79-6941
Virus, Stump-Tailed Macaque
Antigenic Determinants, 79-7003
- Viral Vaccines**
Virus, Avian Reticuloendotheliosis
Immune Response, 79-7068
- Virus, Abelson Murine Leukemia**
Antigens, Viral
Hematopoietic Stem Cells, 79-6974
Immunogenetics, 79-6974
- Virus Activation**
Radiation, Ionizing
Hamster, 79-6915
Virus, C-Type RNA Tumor
Antipain, 79-6893
Radiation, Ionizing, 79-6893
Ultraviolet Rays, 79-6893
Virus, Moloney Murine Leukemia
Cell Differentiation, 79-6986
- Virus, Adeno 2**
Intercistronic Complementation
Temperature Sensitive Mutants
79-7043
T-Lymphocytes
Antilymphocyte Serum, 79-7042
Membrane Proteins
Cells, Cultured, 79-7042
Neoplasms, Experimental
Graft vs Host Reaction, 79-7064
Mouse, Nude, 79-7042
Peptides
Genes, Viral, 79-7043
- Virus, Adeno 4**
Burkitt's Lymphoma
Antibodies, Viral, 79-7013
- Virus, Adeno 5**
Cells, Cultured
Tumorigenicity, 79-7044
Mutation
Colony Formation, 79-7044
RNA, Messenger
Nucleotide Sequence, 79-7045
Peptides, 79-7045
12-*O*-Tetradecanoylphorbol-13-acetate
Cell Transformation, Neoplastic
79-6801
- Virus, Adeno 7**
Virus, Polyoma, BK
Virus, Helper, 79-7032
- Virus, Adeno 12**
Antigens
Cell Membrane, 79-7048
Antigens, Neoplasm
Immune Serums, 79-7047
Protein Kinase, 79-7047
Antigens, Viral
Cell Membrane, 79-7049
Cell Transformation, Neoplastic
79-7049
Transplantation Immunology, 79-7049
DNA Restriction Enzyme
DNA-RNA Hybridization, 79-7046
DNA, Viral
Antigens, Neoplasm, 79-7050
Antigens, Viral, 79-7050
Cell Transformation, Neoplastic
79-7046, 79-7048
Deletion Mutants, 79-7050
Histocompatibility Antigens
Cell Transformation, Neoplastic
79-7048
Transplantation Immunology, 79-7049
Neoplasms, Experimental
Deletion Mutants, 79-7050
Phosphoproteins
IgG, 79-7047
- Virus, AKR Murine Leukemia**
Antigenic Determinants
- Virus, AKR Murine Leukemia (cont'd)**
Antibody Specificity, 79-6957
Cell Transformation, Neoplastic
Thymus Extracts, 79-7069
Chromosomes
Vertical Transmission, 79-6989
Leukemia
Genes, Viral, 79-6989
T-Lymphocytes
Cell Differentiation, 79-7069
Immune Response, 79-7069
RNA, Viral
DNA-RNA Hybridization, 79-6989
- Virus, Avian Leukemia**
Bone Marrow
Cell Differentiation, 79-6929
Hematopoietic Stem Cells
Bone Marrow, 79-6929
Cell Transformation, Neoplastic
79-6928, 79-6929
Replication-Defective Mutants
79-6929
RNA, Viral
DNA-RNA Hybridization, 79-6928
Nucleotide Sequence, 79-6930
Replication-Defective Mutants
79-6928
- Virus, Avian Leukosis**
DNA Polymerase
Antigenic Determinants, 79-6956
Genes, Viral
Crosses, (Genetic), 79-6926
Virus, Pheasant RNA Tumor
Antigenic Determinants, 79-6956
Virus, Recombinant
Subgroup E, 79-6927
Viral Proteins, 79-6927
- Virus, Avian Myelocytomatosis**
RNA, Viral
Nucleotide Sequence, 79-6930
Virus, Helper, 79-6930
Viral Proteins
Cell Transformation, Neoplastic
79-6931
Isolation and Characterization
79-6931
Virus, MC29
Nucleic Acid Homology, 79-6930
- Virus, Avian Reticuloendotheliosis**
Viral Vaccines
Immune Response, 79-7068
Virus, Marek's Disease Herpes
Immunosuppression, 79-7068
- Virus, Avian Sarcoma**
Genes, Viral
Morphological Revertants, 79-6936
Phosphoproteins
Antibody Specificity, 79-6935
Antigenic Determinants, 79-6935
Cell Transformation, Neoplastic
79-6936
Protein Kinase, 79-6936, 79-6937
Vertebrate Cells, 79-6937
Reverse Transcriptase
Temperature Sensitive Mutants
79-6934
Ribonuclease
Temperature Sensitive Mutants
79-6934
Tosyllysine Chloromethyl Ketone
Cell Transformation, Neoplastic
79-6933
Phosphotransferases, ATP, 79-6933
Viral Proteins
Cell Membrane, 79-6932
Cell Transformation, Neoplastic
79-6932
- Virus, B77**
Deletion Mutants
Nucleotide Sequence, 79-6953
Phosphoproteins
Antibody Specificity, 79-6935
RNA, Messenger
- Virus, B77 (cont'd)**
Nucleotide Sequence, 79-6954
RNA, Viral
Polyribosomes, 79-6954
Transformation-Defective Mutants
Virus Replication, 79-6947
- Virus, Baboon C-Type RNA Tumor**
Leukemia, Lymphoblastic
Hybrid Cells, 79-7002
Leukemia, Myeloblastic
Hybrid Cells, 79-7002
Virus Replication
Chromosomes, Human, 6-12, 79-7002
Chromosomes, Human, 19-20, 79-7002
- Virus, Baboon M7**
see Virus, Baboon C-Type RNA Tumor
- Virus, Bovine Papilloma**
DNA, Viral
Cleavage Sites, 79-6998
Endonucleases, 79-6998
Nucleotide Sequence, 79-6996
Virus, Papilloma
Nucleic Acid Homology, 79-6996
- Virus, C-Type RNA Tumor**
Antipain
Virus Activation, 79-6893
Colobus polykomos
Antigenic Determinants, 79-7057
Isolation and Characterization
79-7057
Plasmacytoma
Viral Proteins, 79-6993
Radiation, Ionizing
Antipain, 79-6893
Virus Activation, 79-6893
Virus Replication, 79-7056
Transformation, Genetic
Carcinogenic Potential, Review
79-6635
Ultraviolet Rays
Antipain, 79-6893
Virus Activation, 79-6893
Uridine, 5-Bromo-2'-deoxy-
Antipain, 79-6893
Virus, Radiation Leukemia
Virus Replication, 79-7056
Virus Replication
DNA-RNA Hybridization, 79-7057
- Virus, CELO**
Antigens, Neoplasm
Genes, Viral, 79-7059
Histocompatibility Antigens
Genes, Viral, 79-7059
Neoplasms, Experimental
Hamster, 79-7059
Virus-Like Particles
Cell Transformation, Neoplastic
79-7059
- Virus Cultivation**
Mammary Neoplasms, Experimental
Reverse Transcriptase, 79-6966
Virus, Simian Sarcoma
Virus, Rous Sarcoma, 79-7004
Virus, SV40, 79-7004
- Virus, Cytomegalo**
Adenocarcinoma
Cells, Cultured, 79-7012
Burkitt's Lymphoma
Antibodies, Viral, 79-7013
Colonic Neoplasms
Adenocarcinoma, 79-7012
Ovarian Neoplasms
Theca Cell Tumor, 79-7010
4,4'-Stilbenediol, α, α' -Diethyl-
Virus Replication, 79-7011
Theca Cell Tumor
'Case Report, 79-7010
- Virus, D-Type RNA Tumor**
Antigens, Viral
Isolation and Characterization
79-7058

- Virus, DNA Tumor**
Cells, Cultured
Cell Transformation, Neoplastic
79-7051
- Heart Neoplasms**
Fibrosarcoma, 79-7051
- Kidney Neoplasms**
Carcinoma, 79-7051
- Sarcoma**
Carcinogenic Activity, Hamster
79-7051
- Virus, Epstein-Barr**
Antibody Formation
Cell Transformation, Neoplastic
79-7015
- Breast Neoplasms**
Virus Activation, 79-7019
- Burkitt's Lymphoma**
RNA, Ribosomal, 79-7016
RNA, Viral, 79-7016
- Deoxyribonuclease**
DNA Replication, 79-7014
B-Lymphocytes, 79-7014
- Haptens**
Anti-Antibodies, 79-7015
- IgM**
Cells, Cultured, 79-7015
- Nasopharyngeal Neoplasms**
Antigen-Antibody Reactions, 79-7018
Epidemiology, Taiwan, 79-7141
Seroepidemiology, Cuba, 79-7018
RNA, Viral
DNA-RNA Hybridization, 79-7016
12-*O*-Tetradecanoylphorbol-13-acetate
DNA Replication, 79-7017
- Virus, FBR Murine Sarcoma**
Sarcoma, Osteogenic
Isolation and Characterization
79-6975
Strontium, 79-6975
- Virus, Feline Leukemia**
Immune Serums
Inactivating Factor, 79-7001
- Leukemia**
Seroepidemiology, 79-7163
- Lymphoma**
Seroepidemiology, 79-7163
- Lymphosarcoma**
Urea, Methyl Nitroso-, 79-6999
Urea, Methyl Nitroso-
Immune Response, 79-6999
- Virus, Murine Leukemia**
Antigenic Determinants, 79-6959
- Virus Replication**
T-Lymphocytes, 79-7000
Lymphoid Cells, Human, 79-7000
- Virus, Friend Murine Leukemia**
Anemia
Virus, Helper, 79-6976
- Fibrosarcoma**
Antigens, Neoplasm, 79-6977
Antigens, Viral, 79-6977
Histocompatibility Antigens, 79-6977
- Granulocytes**
Cell Differentiation, 79-7073
- Immune Serums**
Antigen-Antibody Reactions, 79-6977
- Leukemia**
Benzo(a)pyrene, 79-7070
T-Lymphocytes, 79-6980
Precancerous Conditions, 79-6976
- T-Lymphocytes**
Immunity, Cellular, 79-6980
- Polycythemia**
Virus, Helper, 79-6976
- Virus Replication**
Immunogenetics, 79-6978
- Virus, Friend Spleen Focus-Forming**
Virus Replication
Immunogenetics, 79-6978
- Virus, Gazdar Murine Sarcoma**
Viral Proteins
A-Type Particles, 79-6979
- Virus, Gazdar Murine Sarcoma (cont'd)**
Immunoprecipitation, 79-6979
- Virus, Gross Murine Leukemia**
Antigens, Neoplasm
Killer Cells, 79-6980
- Antigens, Viral**
T-Lymphocytes, 79-6981
Neonatal Infection, 79-6981
- Leukemia**
T-Lymphocytes, 79-6980
- T-Lymphocytes**
Histocompatibility Antigens, 79-6980
Immunity, Cellular, 79-6980
- Virus, Herpes Simplex 1**
Co-carcinogenic Effect, 79-7007
- Virus, Guinea Pig Herpes**
Virus Replication
B-Lymphocytes, 79-6995
T-Lymphocytes, 79-6995
- Virus, Harvey Murine Sarcoma-Leukemia**
DNA Restriction Enzyme
Cleavage Sites, 79-6982
- DNA, Viral**
Transformation, Genetic, 79-6982
- Virus, Helper**
Anemia
Virus, Friend Murine Leukemia
79-6976
- Lymphoma**
Virus, Radiation Leukemia, 79-7056
- Polycythemia**
Virus, Friend Murine Leukemia
79-6976
- Virus, Adeno 7**
Virus, Polyoma, BK, 79-7032
- Virus, Avian Myelocytomatosis**
RNA, Viral, 79-6930
- Virus, MC29**
Antigenic Determinants, 79-7060
- Virus, Hepatitis**
Hepatitis
Antigens, Viral, 79-7063
Virus, Woodchuck Hepatitis
Antigenic Determinants, 79-6997
Nucleic Acid Homology, 79-6997
- Virus, Herpes Lucke**
Adenocarcinoma
Epidemiology, 79-7169
- Kidney Neoplasms**
Adenocarcinoma, 79-7169
- Virus, Herpes Saimiri**
Virus, Squirrel Monkey
Coexistence, Mink Lung Cells
79-7005
- Virus, Herpes Simplex**
Skin Neoplasms
Co-carcinogenic Effect, Review
79-6641
4,4'-Stilbenediol, α, α' -Diethyl-
Cell Transformation, Neoplastic
79-7011
Thymidine Kinase, 79-7011
- Virus, Herpes Simplex 1**
Adenocarcinoma
Carcinogenic Activity, Mouse, 79-7007
- Adenosine, 3'-Deoxy-**
Ribonucleotides, 79-7006
- Burkitt's Lymphoma**
Antibodies, Viral, 79-7013
- Lymphoma**
Antigens, Viral, 79-7007
- Mouth Neoplasms**
Carcinoma, Epidermoid, 79-6641
Seroepidemiology, Review, 79-6641
- Ribonucleotides**
DNA Replication, 79-7006
- Salivary Gland Neoplasms**
Adenocarcinoma, 79-7007
- Virus, Gross Murine Leukemia**
Co-carcinogenic Effect, 79-7007
- Virus, Herpes Simplex 2**
Angiosarcoma
Carcinogenic Activity, Mouse, 79-7007
- Carcinoma**
Antigens, Viral, 79-7008
Peptides, 79-7008
- Cervix Neoplasms**
Carcinoma, 79-7008
- Fibrosarcoma**
Antigens, Viral, 79-7007
- Lymphoma**
Antigens, Viral, 79-7007
- Viral Proteins**
Antigen-Antibody Reactions, 79-7009
Isolation and Characterization
79-7009
- Virus, Influenza**
Lung Neoplasms
Benzo(a)pyrene, 79-6633
Carbamic Acid, Ethyl Ester, 79-6633
Co-carcinogenic Effect, Review
79-6633
Diethylamine, *N*-Nitroso-, 79-6633
Smoking, 79-6633
- Virus, Polyoma**
Antineoplastic Activity, 79-7028
Virus Replication, 79-7028
- Virus, Kirsten Murine Leukemia**
Interferon
Cell Transformation, Neoplastic
79-6983
- Virus, Kirsten Murine Sarcoma**
Cholesterol
Cell Transformation, Neoplastic
79-6841
- Fatty Acids**
Cell Transformation, Neoplastic
79-6841
- Virus, Lactate Dehydrogenase**
Hepatitis
Macrophages, 79-7095
- Virus-Like Particles**
Glioblastoma Multiforme
Virus, SV40, 79-7037
- Liver Neoplasms**
Radiation, Ionizing, 79-6915
- Lymphoma**
Virus, Murine Mammary Tumor
79-6965
- Plasmacytoma**
Cell Transformation, Neoplastic
79-7055
- Virus, RNA Tumor, 79-7054**
Prostatic Hypertrophy
Virus, RNA Tumor, 79-7052
- Prostatic Neoplasms**
Virus, RNA Tumor, 79-7052
- Splenic Neoplasms**
Radiation, Ionizing, 79-6915
- Virus, CEO**
Cell Transformation, Neoplastic
79-7059
- Virus, Marek's Disease Herpes**
Immunity, Passive
Killer Cells, 79-6955
- Virus, Avian Reticuloendotheliosis**
Immunosuppression, 79-7068
- Virus, Mason-Pfizer Monkey**
Breast Neoplasms
DNA-RNA Hybridization, 79-6970
- Virus, MC29**
RNA, Viral
Nucleotide Sequence, 79-6930
79-7060
- Virus, Avian Myelocytomatosis**
Nucleic Acid Homology, 79-6930
- Virus, Helper**
Antigenic Determinants, 79-7060
- Virus, Measles**
Burkitt's Lymphoma
Antibodies, Viral, 79-7013

Virus, Moloney Murine Leukemia
 Antigens, Neoplasm
 Antibody Specificity, 79-6987
 Cell Differentiation
 Virus Activation, 79-6986
 Chromosomes
 Vertical Transmission, 79-6989
 Cycloheximide
 Virus Replication, 79-6985
 Leukemia
 Genes, Viral, 79-6989
 Lymphoma
 Antigens, Neoplasm, 79-6987
 Antigens, Viral, 79-6987
 Mammary Neoplasms, Experimental
 79-7071
 RNA, Viral
 DNA Replication, 79-6984
 DNA-RNA Hybridization, 79-6986
 79-6989
 Liver Regeneration, 79-6986
 Poly A, 79-6985
 Polyribosomes, 79-6985
 Reverse Transcription, 79-6984
 RNA, Messenger, 79-6985
 Sarcoma
 T-Lymphocytes, 79-7082
 Virus Replication
 Immunogenetics, 79-6978

Virus, Moloney Murine Sarcoma
 Antibody Formation
 Neoplasm Regression, Spontaneous
 79-7072
 Concanavalin A
 Immune Response, 79-7080
 Erythroleukemia
 Anti-Antibodies, 79-6988
 Immune Serums
 IgG, 79-7072
 IgM, 79-7072
 Interferon
 Anti-Antibodies, 79-6988
 Sarcoma
 Anti-Antibodies, 79-6988

Virus, Murine C-Type Myeloma
 Viral Proteins
 Isolation and Characterization
 79-6993
 Virus, Murine Leukemia
 Antigenic Determinants, 79-6993

Virus, Murine Leukemia
 Antibodies, Viral
 Hybrid Cells, 79-6959
 Antigenic Determinants
 Antibody Specificity, 79-6959
 Autoantibodies
 Immunogenetics, 79-7097
 Glomerulonephritis
 Autoantibodies, 79-7097
 Immune Serums
 Inactivating Factor, 79-7001
 Lipoproteins, 79-7001
 Mammary Neoplasms, Experimental
 Antigens, Viral, 79-6967
 Plasmacytoma
 A-Type Particles, 79-7053
 RNA, Viral
 Liver Regeneration, 79-6986
 Sarcoma, Reticulum Cell
 Autoantibodies, 79-7097
 Viral Proteins
 Antibody Specificity, 79-6957
 Host Range, 79-6958
 Radioimmunoassay, 79-6958
 Virus, Feline Leukemia
 Antigenic Determinants, 79-6959
 Virus, Murine C-Type Myeloma
 Antigenic Determinants, 79-6993
 Virus, Recombinant
 Inactivating Factor, 79-7001

Virus, Murine Mammary Tumor
 Adenocarcinoma
 Phosphoproteins, 79-6962
 Antibodies, Viral

Virus, Murine Mammary Tumor(cont'd)
 Antigenic Determinants, 79-6971
 Strain Difference, 79-6971
 Antigens, Viral
 Milk, 79-6972, 79-6973
 Rabbit, Rat, 79-6973
 Benz(a)anthracene, 7,12-Dimethyl-
 RNA, Viral, 79-6969
 Breast Neoplasms
 Carcinoma, Ductal, 79-6968
 DNA-RNA Hybridization, 79-6970
 Carcinoma, Ductal
 Virus Replication, 79-6968
 DNA, Viral
 Endonucleases, 79-6961
 Vertical Transmission, 79-6961
 Lymphoma
 Peptides, 79-6965
 Virus-Like Particles, 79-6965
 Mammary Neoplasms, Experimental
 Antibodies, Viral, 79-6971
 Antigens, Viral, 79-6967, 79-6972
 Benz(a)anthracene, 7,12-Dimethyl-
 79-6969
 Cell Line, 79-6966
 Glucocorticoids, 79-6963
 Horizontal Transmission, 79-6972
 Hybrid Cells, 79-7071
 Peptides
 Protein Kinase, 79-6962
 RNA, Viral
 Glucocorticoids, 79-6963
 Prolactin, 79-6963
 Viral Proteins
 Antigenic Determinants, 79-6964

Virus, Murine Sarcoma
 Immunosuppression
 Leukocyte Culture Test, Mixed
 79-6960
 Interferon
 Cell Transformation, Neoplastic
 79-6983
 T-Lymphocytes
 Antilymphocyte Serum, 79-6960
 Suppressor Cells, 79-6960
 Neoplasms, Experimental
 Immunity, Cellular, 79-7065
 Sarcoma
 Immunosuppression, 79-6960

Virus, Myeloma-Associated
 Plasmacytoma
 A-Type Particles, 79-7053, 79-7054

Virus, Newcastle Disease
 Antigens, Viral
 Immunologic Technics, 79-7061
 Lymphoma
 Cell Membrane, 79-7061
 Membrane Proteins
 Hemolysis, 79-7061

Virus, Papilloma
 DNA, Viral
 Nucleotide Sequence, 79-6996
 Skin Neoplasms
 Genetics, 79-7030
 Virus, Bovine Papilloma
 Nucleic Acid Homology, 79-6996
 Virus, Shope Rabbit Papilloma
 Nucleic Acid Homology, 79-6996

Virus, Papova
 Paraganglioma
 DNA, Viral, 79-7020
 Isolation and Characterization
 79-7020

Virus, Pheasant RNA Tumor
 DNA Polymerase
 Antigenic Determinants, 79-6956
 Radioimmunoassay, 79-6956
 Virus, Avian Leukosis
 Antigenic Determinants, 79-6956

Virus, Polyoma
 Antigens, Neoplasm
 Cell Membrane, 79-7029

Virus, Polyoma(cont'd)
 Nucleotide Sequence, 79-7024
 Cell Transformation, Neoplastic
 Deletion Mutants, 79-7021, 79-7026
 DNA Restriction Enzyme
 Deletion Mutants, 79-7026
 DNA, Viral
 Antigens, Neoplasm, 79-7021
 Binding Sites, 79-7025
 Deletion Mutants, 79-7021, 79-7023
 Nucleic Acid Conformation, 79-7022
 Nucleotide Sequence, 79-7024
 RNA, Messenger, 79-7024
 Membrane Proteins
 Cell Transformation, Neoplastic
 79-7029
 RNA, Messenger
 Deletion Mutants, 79-7023
 DNA-RNA Hybridization, 79-7022
 79-7027
 RNA, Viral
 DNA-RNA Hybridization, 79-7027
 Viral Proteins
 Binding Sites, 79-7025
 Virus, Influenza
 Antineoplastic Activity, 79-7028
 Virus Replication, 79-7028

Virus, Polyoma, BK
 DNA, Viral
 Nucleotide Sequence, 79-7031
 Medulloblastoma
 Histologic Study, Hamster, 79-7033
 Virus, Adeno 7
 Virus, Helper, 79-7032
 Virus Replication
 CV-1 Monkey Cells, 79-7032
 Virus, SV40
 Antigenic Determinants, 79-7032
 Nucleic Acid Homology, 79-7031

Virus, Radiation Leukemia
 Lymphoma
 Virus, Helper, 79-7056
 Virus, C-Type RNA Tumor
 Virus Replication, 79-7056

Virus, Rat Leukemia
 RNA, Messenger
 Stress, Anaerobic, 79-6994
 Virus Replication, 79-6994

Virus, Rauscher Murine Leukemia
 Amino Acids
 Binding Sites, 79-6992
 Antigenic Determinants
 Immunity, Cellular, 79-6991
 Glycoproteins
 Binding Sites, 79-6992
 Cell Membrane, 79-6992
 Histocompatibility Antigens
 T-Lymphocytes, 79-6991
 Viral Proteins, 79-6991
 Leukemia
 T-Lymphocytes, 79-6980
 T-Lymphocytes
 Immunity, Cellular, 79-6980
 Phosphoproteins
 Amino Acids, 79-6990
 Viral Proteins
 Antigenic Determinants, 79-6990

Virus, Recombinant
 Virus, Avian Leukosis
 Subgroup E, 79-6927
 Viral Proteins, 79-6927
 Virus, Murine Leukemia
 Inactivating Factor, 79-7001
 Virus, Rous Sarcoma
 Nucleotide Sequence, 79-6943

Virus Replication
 Carcinoma, Ductal
 Virus, Murine Mammary Tumor
 79-6968
 Glioma
 Virus, Simian Sarcoma, 79-7004
 HeLa Cells
 Virus, Simian Sarcoma, 79-7004

Virus Replication (cont'd)

- Virus, B77
 - Transformation-Defective Mutants 79-6947
- Virus, Baboon C-Type RNA Tumor
 - Chromosomes, Human, 6-12, 79-7002
 - Chromosomes, Human, 19-20, 79-7002
- Virus, C-Type RNA Tumor
 - DNA-RNA Hybridization, 79-7057
 - Radiation, Ionizing, 79-7056
- Virus, Cytomegalo
 - 4,4'-Stilbenediol, α, α' -Diethyl- 79-7011
- Virus, Feline Leukemia
 - T-Lymphocytes, 79-7000
 - Lymphoid Cells, Human, 79-7000
- Virus, Friend Murine Leukemia
 - Immunogenetics, 79-6978
- Virus, Friend Spleen Focus-Forming
 - Immunogenetics, 79-6978
- Virus, Guinea Pig Herpes
 - B-Lymphocytes, 79-6995
 - T-Lymphocytes, 79-6995
- Virus, Moloney Murine Leukemia
 - Cycloheximide, 79-6985
 - Immunogenetics, 79-6978
- Virus, Polyoma
 - Virus, Influenza, 79-7028
- Virus, Polyoma, BK
 - CV-1 Monkey Cells, 79-7032
- Virus, Radiation Leukemia
 - Virus, C-Type RNA Tumor, 79-7056
- Virus, Rat Leukemia
 - RNA, Messenger, 79-6994
- Virus, Rous Sarcoma
 - Cell Cycle Kinetics, 79-6940
 - Cell Transformation, Neoplastic 79-6940
 - Transformation-Defective Mutants 79-6947
 - Transformation, Genetic, 79-6946
- Virus, RNA Tumor
 - Paranglioma
 - Isolation and Characterization 79-7020
 - Plasmacytoma
 - Virus-Like Particles, 79-7054
 - Prostatic Hypertrophy
 - Reverse Transcriptase, 79-7052
 - Virus-Like Particles, 79-7052
 - Prostatic Neoplasms
 - Virus-Like Particles, 79-7052
- Virus, Rous-Associated
 - Pactamycin
 - Antigenic Determinants, 79-6948
 - Viral Proteins
 - Antigenic Determinants, 79-6948
- Virus, Avian Leukosis
 - Virus, Recombinant, 79-6927
- Virus, Rous Sarcoma
 - Acetylcholinesterase
 - Cell Cycle Kinetics, 79-6945
 - Antigen-Antibody Complex
 - Immunoprecipitation, 79-6951
 - Antigenic Determinants
 - Virus Rescue, 79-6949
 - Antigens, Neoplasm
 - Cell Membrane, 79-6950
 - Cell Transformation, Neoplastic 79-6951
 - Immunity, Cellular, 79-6952
 - Immunoprecipitation, 79-6951
 - Antigens, Viral
 - Antibody Formation, 79-6952
 - Antilymphocyte Serum
 - Tumor Latency, 79-6942
 - Cell Fusion
 - Replication-Defective Mutants 79-6949
 - Cell Transformation, Neoplastic
 - Temperature Sensitive Mutants 79-6945
 - Deletion Mutants
 - Carcinogenic Activity, Quail, 79-6943
 - Dibutyl Cyclic AMP

Virus, Rous Sarcoma (cont'd)

- Cell Transformation, Neoplastic 79-6950
- DNA, Circular
 - DNA Replication, 79-6944
- DNA, Viral
 - Virus Rescue, 79-6946
- Homocysteine, S-Adenosyl-
 - Protein Arginine Methyltransferase 79-6939
- Immunity, Passive
 - Tumor Latency, 79-6942
- T-Lymphocytes
 - Antilymphocyte Serum, 79-6942
- Myosin
 - Cell Differentiation, 79-6945
- Plant Agglutinins
 - Lymphocyte Transformation, 79-6952
- Protein Arginine Methyltransferase
 - Cell Transformation, Neoplastic 79-6939
- RNA Polymerase
 - DNA Replication, 79-6938
 - Isolation and Characterization 79-6938
- Sarcoma
 - Immunologic Technics, 79-6942
 - RNA Polymerase, 79-6938
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - Cell Transformation, Neoplastic 79-6950
- Viral Proteins
 - Antigenic Determinants, 79-6941
 - Glucose, 2-Deoxy-, 79-6941
 - Tunicamycin, 79-6941
- Virus, Recombinant
 - Nucleotide Sequence, 79-6943
- Virus Replication
 - Cell Cycle Kinetics, 79-6940
 - Cell Transformation, Neoplastic 79-6940
 - Transformation-Defective Mutants 79-6947
 - Transformation, Genetic, 79-6946
- Virus, Simian Sarcoma
 - Virus Cultivation, 79-7004
- Virus, Sendai
 - Antigens, Viral
 - Immunologic Technics, 79-7061
 - Lymphoma
 - Cell Membrane, 79-7061
 - Membrane Proteins
 - Hemolysis, 79-7061
- Virus, Shope Rabbit Papilloma
 - DNA, Viral
 - Nucleotide Sequence, 79-6996
 - Virus, Papilloma
 - Nucleic Acid Homology, 79-6996
- Virus, Simian Sarcoma
 - Glioma
 - Virus Replication, 79-7004
 - HeLa Cells
 - Virus Replication, 79-7004
 - Virus, Rous Sarcoma
 - Virus Cultivation, 79-7004
 - Virus, SV40
 - Virus Cultivation, 79-7004
- Virus, Squirrel Monkey
 - Virus, Herpes Saimiri
 - Coexistence, Mink Lung Cells 79-7005
- Virus, Stump-Tailed Macaque
 - DNA, Viral
 - Nucleotide Sequence, 79-7003
 - Viral Proteins
 - Antigenic Determinants, 79-7003
 - Virus, SV40
 - DNA-DNA Hybridization, 79-7003
- Virus, SV40
 - Antigens, Neoplasm
 - Cells, Cultured, 79-7035
 - Deletion Mutants, 79-7036, 79-7038
 - Immunoprecipitation, 79-7034

Virus, SV40 (cont'd)

- Isolation and Characterization 79-7038
- RNA, Messenger, 79-7034
- Cell Fusion
 - Virus Rescue, 79-7035
- DNA Restriction Enzyme
 - Chromosome Analysis, 79-6634
 - Transformation, Genetic, Review 79-6634
- DNA, Viral
 - Mutation, Review, 79-6634
- Fibrosarcoma
 - Deletion Mutants, 79-7036
- Glioblastoma Multiforme
 - Antigens, Neoplasm, 79-7037
 - Virus-Like Particles, 79-7037
- Histocompatibility Antigens
 - Immunogenetics, 79-7040
 - Transplantation Immunology, 79-7040
- Liver Neoplasms
 - Sarcoma, 79-7041
- Lung Neoplasms
 - Adenocarcinoma, Papillary, 79-7041
 - Adenoma, 79-7041
- Meningioma
 - Antigens, Neoplasm, 79-7039
- Plasmodium berghei yoelii*
 - Immunosuppression, 79-7041
- Sarcoma
 - Histocompatibility Antigens, 79-7040
 - Liver Neoplasms, 79-7041
- Splenic Neoplasms
 - Sarcoma, 79-7041
- Virus, Polyoma, BK
 - Antigenic Determinants, 79-7032
 - Nucleic Acid Homology, 79-7031
- Virus, Simian Sarcoma
 - Virus Cultivation, 79-7004
- Virus, Stump-Tailed Macaque
 - DNA-DNA Hybridization, 79-7003
- Virus, Woodchuck Hepatitis
 - Australia Antigen
 - Antigens, Viral, 79-6997
 - Virus, Hepatitis
 - Antigenic Determinants, 79-6997
 - Nucleic Acid Homology, 79-6997
- Water Pollution
 - Skin Neoplasms
 - Arsenic, 79-6644
- Wounds and Injuries
 - Carcinoma 256, Walker
 - Neoplasm Metastasis, 79-6657
 - Turpentine, 79-6657
 - Hodgkin's Disease
 - Axilla, 79-7153
 - Lung Neoplasms
 - Neoplasm Metastasis, 79-6657
- Xeroderma Pigmentosum
 - Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - DNA Repair, 79-6873
 - Butane, 1,2:3,4-Diepoxy-
 - Chromosome Aberrations, 79-6670
 - Complementation Group
 - Diagnosis and Prognosis, 79-6875
 - DNA Repair
 - Complementation Group, 79-6875
 - Fibroblasts, 79-6875
 - Radiation, Ionizing
 - Chromosome Aberrations, 79-6629
 - DNA Repair, 79-6629
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - Peptides, 79-6799
 - Ultraviolet Rays
 - DNA Repair, 79-6629, 79-6873
 - 79-6875, 79-6877, 79-6890

Zearalenone
Esophageal Neoplasms
Food Contamination, 79-7182

Zinc Chloride
Calcium
Chromosome Aberrations, 79-6646

Zirconium Dioxide
Lung Neoplasms
Inhalation Study, Hamster, 79-6921

LIBRARY U. OF I. URBANA - CHAMPAIGN

Chemical Abstracts Service Registry Number Index

- 50-00-0, 79-6742
50-02-2, 79-6794
50-03-3, 79-7083
50-06-6, 79-6687, 79-6742, 79-6746
79-6819
50-18-0, 79-6686, 79-6744, 79-6771
79-6866
50-28-2, 79-6819, 79-6852, 79-6853
79-7137
50-29-3, 79-6609
50-32-8, 79-6609, 79-6633, 79-6678
79-6807, 79-6815, 79-6829, 79-6830
79-6831, 79-6832, 79-6833, 79-6834
79-6835, 79-6836, 79-6837, 79-6839
79-6840, 79-7070, 79-7159
50-76-0, 79-7192, 79-7194
50-78-2, 79-6795
50-81-7, 79-6681
51-21-8, 79-6738
51-31-0, 79-6800, 79-6819
51-75-2, 79-6723
51-79-6, 79-6633, 79-6698, 79-6699
52-24-4, 79-6785
52-90-4, 79-6707
53-03-2, 79-7155
53-42-9, 79-7150
53-43-0, 79-7150
53-70-3, 79-6807, 79-6819
53-86-1, 79-6795, 79-6803
53-94-1, 79-6691
53-95-2, 79-6679, 79-6681, 79-6864
53-96-3, 79-6679, 79-6682, 79-6683
79-6684, 79-6685, 79-6686, 79-6687
79-6688, 79-6744, 79-7122, 79-7123
54-05-7, 79-6876
54-85-3, 79-6616
55-18-5, 79-6609, 79-6633, 79-6678
79-6722, 79-6724, 79-6725, 79-6812
79-6862, 79-7123
55-38-9, 79-6654
55-80-1, 79-6756, 79-6757
55-91-4, 79-6865
56-38-2, 79-6765
56-49-5, 79-6679, 79-6687, 79-6744
79-6746, 79-6761, 79-6808, 79-6819
79-6821, 79-6822, 79-6823, 79-6824
79-6825, 79-6826, 79-6827, 79-6828
79-6830, 79-6883, 79-6907, 79-7066
79-7070, 79-7080, 79-7082
56-53-1, 79-6602, 79-6619, 79-6620
79-6679, 79-6703, 79-6846, 79-6847
79-6849, 79-6850, 79-6851, 79-6852
79-7011, 79-7174
56-55-3, 79-6819
56-57-5, 79-6743, 79-6744
56-75-7, 79-6622, 79-6757
56-86-0, 79-6737
57-30-7, 79-6675
57-57-8, 79-6700
57-63-6, 79-6856
57-83-0, 79-6857
57-85-2, 79-6853
57-88-5, 79-6841, 79-6888, 79-7197
57-97-6, 79-6618, 79-6667, 79-6744
79-6800, 79-6802, 79-6803, 79-6804
79-6807, 79-6808, 79-6809, 79-6810
79-6811, 79-6812, 79-6813, 79-6814
79-6815, 79-6816, 79-6817, 79-6818
79-6823, 79-6830, 79-6850, 79-6857
79-6864, 79-6871, 79-6963, 79-6969
58-08-2, 79-6876, 79-6891, 79-7177
58-22-0, 79-6849
58-39-9, 79-7198
58-55-9, 79-6876
58-61-7, 79-6740
59-05-2, 79-6783
59-14-3, 79-6893
59-89-2, 79-6612
59-92-7, 79-7195
60-57-1, 79-6609
60-92-4, 79-6800, 79-7194
61-19-8, 79-7196
61-57-4, 79-6868
62-44-2, 79-6615
62-49-7, 79-6683
62-50-0, 79-6649, 79-6700, 79-6899
79-7044, 79-7187
62-68-0, 79-6819
62-75-9, 79-6608, 79-6698, 79-6704
79-6721, 79-6722, 79-6734, 79-6863
79-6864
63-05-8, 79-7150
63-25-2, 79-6812
64-17-5, 79-6640, 79-6661, 79-6761
79-7181
65-86-1, 79-6788
66-27-3, 79-6700
66-81-9, 79-6821, 79-6985, 79-7194
67-73-2, 79-6803
67-97-0, 79-6819
68-26-8, 79-6842, 79-6843, 79-6900
69-57-8, 79-6823
70-25-7, 79-6700, 79-6866, 79-7044
79-7129
70-70-2, 79-6851
71-43-2, 79-6761, 79-7176
71-58-9, 79-6854
72-56-0, 79-6665
73-03-0, 79-7006
74-96-4, 79-6664
75-01-4, 79-6662, 79-6663
75-07-0, 79-6661, 79-6678
75-35-4, 79-6666
75-47-8, 79-6659
75-56-9, 79-6744
77-79-2, 79-6778
78-89-7, 79-6666
78-93-3, 79-7165
79-81-2, 79-6845
80-08-0, 79-6613
82-28-0, 79-6792
83-44-3, 79-6631
84-16-2, 79-7174
84-17-3, 79-6851, 79-7174
85-30-3, 79-6740
85-44-9, 79-6762
86-30-6, 79-6730
86-50-0, 79-6777
87-66-1, 79-6784
87-86-5, 79-6774
88-06-2, 79-6747
91-59-8, 79-6771, 79-6822
91-93-0, 79-6769
92-67-1, 79-6768
93-76-5, 79-6677, 79-6774
94-59-7, 79-6609, 79-6614, 79-6748
95-06-7, 79-6702
95-56-7, 79-6746
95-79-4, 79-6751
96-12-8, 79-6666, 79-6668
98-86-2, 79-6742
100-44-7, 79-6740
100-52-7, 79-6742
100-75-4, 79-6612, 79-6721
103-33-3, 79-6766
103-85-5, 79-6718
103-90-2, 79-6616
105-11-3, 79-6763
106-41-2, 79-6746
106-89-8, 79-6744
106-93-4, 79-6664, 79-6666
107-05-1, 79-6666, 79-6669
107-20-0, 79-6739
108-10-1, 79-7165
108-86-1, 79-6746
108-88-3, 79-6761
111-02-4, 79-7197
111-44-4, 79-6739
114-26-1, 79-6812
115-02-6, 79-6683
115-09-3, 79-6651

- 116-06-3, 79-6780, 79-6812
 116-31-4, 79-6843
 120-61-6, 79-6749
 120-62-7, 79-6760
 120-71-8, 79-6755
 121-25-5, 79-6735
 123-93-3, 79-6739
 126-07-8, 79-6785
 127-47-9, 79-6843, 79-6853
 128-37-0, 79-6674, 79-6698, 79-6699
 79-6753
 128-66-5, 79-6820
 129-00-0, 79-6815
 131-48-6, 79-6817
 135-20-6, 79-6754
 139-94-6, 79-6713
 140-56-7, 79-6656
 140-67-0, 79-6614
 142-46-1, 79-6717
 143-50-0, 79-6782
 146-59-8, 79-6723
 148-82-3, 79-7155
 150-97-0, 79-7197
 153-78-6, 79-6842
 154-17-6, 79-6941
 154-93-8, 79-7155
 156-62-7, 79-6647
 189-55-9, 79-6761
 192-97-2, 79-6815
 206-44-0, 79-6815
 215-58-7, 79-6807
 218-01-9, 79-6861
 297-99-4, 79-6655
 298-00-0, 79-6741
 298-81-7, 79-6071, 79-6287, 79-6359
 79-6872
 302-79-4, 79-6843, 79-6889
 303-33-3, 79-6776
 303-34-4, 79-6776
 333-41-5, 79-6764
 352-97-6, 79-6706
 362-74-3, 79-6950
 372-75-8, 79-6607
 398-32-3, 79-6689
 446-86-6, 79-6781
 479-68-5, 79-6667
 521-18-6, 79-6853
 540-51-2, 79-6664
 540-73-8, 79-6631, 79-6673, 79-6674
 79-6675, 79-6768
 542-75-6, 79-6666
 546-67-8, 79-6646, 79-6689
 551-92-8, 79-6735
 558-13-4, 79-6666
- 569-77-7, 79-6784
 578-76-7, 79-6704, 79-6709, 79-6865
 590-21-6, 79-6666
 592-62-1, 79-6675, 79-6768
 604-59-1, 79-6804, 79-6819
 607-30-7, 79-6767
 610-49-1, 79-6761
 613-13-8, 79-6761
 613-47-8, 79-6767
 614-95-9, 79-6701
 615-53-2, 79-6700, 79-6812
 621-64-7, 79-6694, 79-6721, 79-6729
 625-52-5, 79-6703
 636-21-5, 79-6752
 638-23-3, 79-6739
 646-14-0, 79-6693
 671-16-9, 79-6243, 79-6244, 79-6299
 79-6750
 684-93-5, 79-6607, 79-6618, 79-6700
 79-6704, 79-6705, 79-6707, 79-6708
 79-6709, 79-6710, 79-6867, 79-6999
 759-73-9, 79-6607, 79-6608, 79-6609
 79-6618, 79-6651, 79-6703, 79-6707
 79-6712, 79-6714, 79-6715, 79-6716
 797-63-7, 79-6856
 816-57-9, 79-6607, 79-6707
 838-95-9, 79-6848
 869-01-2, 79-6607
 915-67-3, 79-6791
 924-16-3, 79-6721, 79-6733
 924-46-9, 79-6721
 930-55-2, 79-6612, 79-6734
 932-83-2, 79-6612, 79-6721
 937-40-6, 79-6742
 961-07-9, 79-6691
 968-81-0, 79-6720
 979-92-0, 79-6939
 999-81-5, 79-6676
 1067-33-0, 79-6775
 1095-90-5, 79-6671
 1116-54-7, 79-6611, 79-6695, 79-6696
 79-6734
 1145-73-9, 79-6848
 1156-19-0, 79-6719
 1162-65-8, 79-6609, 79-6787, 79-6788
 79-6790, 79-6791, 79-6859
 1309-37-1, 79-6824, 79-6825, 79-6831
 79-6922
 1314-20-1, 79-6770
 1314-23-4, 79-6921
 1317-79-9, 79-6831
 1332-21-4, 79-6640, 79-6650, 79-6824
 79-6825, 79-6831
 1385-95-1, 79-6789
 1401-55-4, 79-6786
 1403-66-3, 79-6823
- 1405-46-5, 79-6948
 1456-28-6, 79-6612, 79-6745, 79-7125
 1464-53-5, 79-6670, 79-6744
 1746-01-6, 79-6773, 79-6813, 79-6819
 1910-42-5, 79-6698, 79-6758
 1912-31-8, 79-3725
 1912-32-9, 79-6700
 1921-70-6, 79-6672
 2243-62-1, 79-6772
 2338-05-8, 79-6924
 2364-87-6, 79-6933
 2489-77-2, 79-6711
 2498-77-3, 79-6806
 2764-72-9, 79-6758
 3067-13-8, 79-6836
 3067-14-9, 79-6836
 3308-64-3, 79-6828
 3343-12-2, 79-6828
 3522-50-7, 79-6924
 3688-53-7, 79-6690
 3715-92-2, 79-6736
 3817-11-6, 79-6721, 79-6731, 79-6732
 79-6733, 79-6849
 3871-20-3, 79-6681
 4251-85-8, 79-6723
 4549-44-4, 79-6729
 4759-48-2, 79-6844
 5273-86-9, 79-6614
 6051-87-2, 79-6687, 79-6746, 79-6819
 6098-44-8, 79-6680, 79-6691, 79-6848
 79-6873, 79-6891
 6219-71-2, 79-6759
 6281-23-8, 79-6697
 6795-23-9, 79-6789
 6804-07-5, 79-6735
 6810-26-0, 79-6767
 7227-91-0, 79-6709
 7390-95-6, 79-6828
 7439-92-1, 79-7176
 7440-02-0, 79-7143, 79-7144, 79-7145
 7440-08-6, 79-6922
 7440-16-6, 79-6896
 7440-18-8, 79-6896
 7440-38-2, 79-6644
 7440-44-0, 79-6806
 7440-70-2, 79-6646
 7632-00-0, 79-6607, 79-6651, 79-6703
 7646-85-7, 79-6646
 7681-76-7, 79-6735
 7718-54-9, 79-6652
 7773-01-5, 79-6652
 7778-50-9, 79-6923
 7782-44-7, 79-6871, 79-6894

7782-49-2, 79-6685
 7782-77-6, 79-6692, 79-6693, 79-6694
 7782-79-8, 79-6899
 7787-47-5, 79-6652
 8001-30-7, 79-6817
 8002-05-9, 79-6672
 8006-64-2, 79-6657
 8015-30-3, 79-6854
 9001-12-1, 79-6795
 9001-45-0, 79-6768, 79-7090
 9001-63-2, 79-6796
 9001-78-9, 79-6733
 9002-62-4, 79-6811, 79-6818, 79-6858
 79-6963, 79-7137, 79-7198
 9002-71-5, 79-6811
 9002-72-6, 79-6811
 9003-98-9, 79-7014
 9004-10-8, 79-7187, 79-7200
 9004-54-0, 79-6657
 9007-27-6, 79-7199
 9008-11-1, 79-6983, 79-6988
 9008-18-8, 79-6833
 9013-80-3, 79-6657
 9035-50-1, 79-6616, 79-6689
 9044-66-0, 79-6657
 10108-64-2, 79-6645, 79-6646
 11028-71-0, 79-7080
 11056-06-7, 79-6904
 11089-65-9, 79-6941
 11097-69-1, 79-6813
 11104-36-2, 79-6657
 11118-26-6, 79-6941
 11121-03-2, 79-6657
 12001-28-4, 79-6640, 79-6650, 79-6824
 79-6825, 79-6831
 12001-29-5, 79-6640, 79-6650, 79-6824
 79-6825, 79-6831
 12035-72-2, 79-6652
 12059-95-9, 79-6921

12172-73-5, 79-6640, 79-6650, 79-6824
 79-6825, 79-6831
 12407-86-2, 79-6812
 12587-46-1, 79-6921
 12626-85-6, 79-6657
 13256-11-6, 79-6742
 13256-13-8, 79-6610
 13256-32-1, 79-6867
 13345-21-6, 79-6836
 13394-86-0, 79-6768
 13743-07-2, 79-6712
 13823-27-3, 79-6923
 13967-73-2, 79-6975
 13981-16-3, 79-6923, 79-6924
 14047-09-7, 79-6813
 14301-11-2, 79-6848
 15356-70-4, 79-6660
 16238-56-5, 79-6805
 16320-04-0, 79-6857
 16338-97-9, 79-6610
 16543-55-8, 79-6611
 16561-29-8, 79-6666, 79-6794, 79-6795
 79-6796, 79-6797, 79-6798, 79-6799
 79-6800, 79-6801, 79-6809, 79-6813
 79-6827, 79-6872, 79-6883, 79-6950
 79-7017
 16812-54-7, 79-6652
 17068-78-9, 79-6640, 79-6650, 79-6824
 79-6825, 79-6831
 17924-92-4, 79-7182
 19010-66-3, 79-6648
 19530-88-2, 79-6724, 79-6862
 20535-83-5, 79-6704, 79-6709, 79-6865
 20917-49-1, 79-6612
 20941-65-5, 79-6658
 21561-99-9, 79-6867
 22225-32-7, 79-6685
 23214-92-8, 79-6842
 23255-93-8, 79-6779
 23668-11-3, 79-6948

24201-58-9, 79-6687
 24554-26-5, 79-6733
 24928-17-4, 79-6797, 79-6809
 24961-39-5, 79-6805
 25013-16-5, 79-6832
 25843-45-2, 79-6768, 79-6860
 26628-22-8, 79-6899
 28622-84-6, 79-6834, 79-6836
 33857-26-0, 79-6774, 79-6813
 34807-41-5, 79-6268, 79-6272, 79-6277
 37224-17-2, 79-6657
 37301-45-4, 79-6812
 37317-41-2, 79-6687
 37691-11-5, 79-6893
 39603-53-7, 79-6721
 39603-54-8, 79-7125
 40542-65-2, 79-6857
 49606-40-8, 79-6707
 51866-19-4, 79-6724
 53609-64-6, 79-6721, 79-6726, 79-6727
 56856-83-8, 79-6865
 57117-24-5, 79-6812
 57303-99-8, 79-6836
 59963-01-8, 79-6815, 79-6834
 60239-58-9, 79-6848
 60391-92-6, 79-6706
 60454-72-0, 79-6657
 60599-38-4, 79-6728
 60666-36-6, 79-6779
 62080-78-8, 79-6851
 62593-23-1, 79-6812
 64005-62-5, 79-6701
 67175-75-1, 79-6861
 67175-77-3, 79-6861

Wiswesser Line Notation Index

.AS, 79-6644
 .BE..G2, 79-6652
 .C, 79-6806
 .CA, 79-6646
 .CA..NCN, 79-6647
 .CD..G2, 79-6645, 79-6646
 .FE2.O3, 79-6824, 79-6825, 79-6831
 79-6922
 .KA2.CR2-O5-Q2, 79-6923
 .MN..G2, 79-6652
 .NA..N-O-Q, 79-6607, 79-6651, 79-6703
 .NI, 79-7143, 79-7144, 79-7145
 .NI..G2, 79-6652
 .NI3.S2, 79-6652
 .PB, 79-7176
 .PO, 79-6922
 .PU 79-6923, 79-6924
 .PU..N-O4, 79-6923
 .PU..O2, 79-6921
 .RH, 79-6896
 .RU, 79-6896
 .SE, 79-6685
 .SI..O2, 79-6831
 .SR, 79-6975
 .TH..O2, 79-6770
 .ZN..G2, 79-6646
 .ZR..O2, 79-6921
 ER, 79-6746
 EXEEE, 79-6666
 EYR&UYR&R D2, 79-6667
 E2, 79-6664
 E2E, 79-6664, 79-6666
 E2Q, 79-6664
 FR DR, 79-6689
 G-HG-1, 79-6651
 GXGGYR DG&R DG, 79-6609
 GYGU1, 79-6666
 GIR, 79-6740
 GIU1, 79-6662, 79-6663
 GIU2, 79-6666
 GIYE1E, 79-6666, 79-6668
 G2K1&1&1 &G, 79-6676
 G2N1&2G, 79-6723
 G2O2G, 79-6739
 G2U1, 79-6666, 79-6669
 G2U1G, 79-6666
 IVR, 79-6742
 IYII, 79-6659
 L B656 HHJ DNQV1, 79-6685
 L B656 HHJ EMQ, 79-6691

L B656 HHJ EMV1, 79-6679, 79-6682
 79-6683, 79-6684, 79-6685, 79-6686
 79-6687, 79-6688, 79-6744, 79-7122
 79-7123
 L B656 HHJ ENOV1&V1, 79-6680
 79-6691, 79-6848, 79-6873, 79-6891
 L B656 HHJ ENQV1, 79-6679, 79-6681
 79-6864
 L B656J HHJ EZ, 79-6842
 L C6566 1A PJ, 79-6815
 L C666 BV IVJ DZ E1, 79-6792
 L C666J DZ, 79-6761
 L C666J EZ, 79-6761
 L D6 B66 P666 2AB A&J, 79-6761
 L D6 B666J, 79-6819
 L D6 B666J C1 J1, 79-6618, 79-6667
 79-6744, 79-6800, 79-6802, 79-6803
 79-6804, 79-6807, 79-6808, 79-6809
 79-6810, 79-6811, 79-6812, 79-6813
 79-6814, 79-6815, 79-6816, 79-6817
 79-6818, 79-6823, 79-6830, 79-6850
 79-6857, 79-6864, 79-6871, 79-6963
 79-6969
 L D6 B666J C1 J1E, 79-6805
 L D6 B666J J1E, 79-6805
 L D6 B666J R1, 79-6806
 L D6 B6666 2AB TJ, 79-6609, 79-6633
 79-6678, 79-6807, 79-6815, 79-6829
 79-6830, 79-6831, 79-6832, 79-6833
 79-6834, 79-6835, 79-6836, 79-6837
 79-6839, 79-6840, 79-7070, 79-7159
 L D6 B6666 2AB TJ GQ HQ, 79-6836
 L D6 B6666 2AB TJ LQ MQ, 79-6834
 79-6836
 L D6 B6666 2AB TJ OQ, 79-6836
 L D6666 B6 2AB TJ, 79-6815
 L E5 B666 FV OV MUTJ A1 E1, 79-7150
 L E5 B666 LUTJ A1 E1 FY&3Y QQ -
 B&AEFO, 79-6841, 79-6888, 79-7197
 L E5 B666 OV AHTTT&J A1 CQ E1
 FV1Q FQ G1 -A&B -B&ACEFG
 79-6794
 L E5 B666 OV MUTJ A1 COV1 E1 FV1
 L -A&L -B&ACEF
 79-6854
 L E5 B666 OV MUTJ A1 CQ E1 FV2VQ
 FQ -B&ACEF, 79-7083
 L E5 B666 OV MUTJ A1 E1 FQ -B&AEF
 79-6849
 L E5 B666 OV MUTJ A1 E1 FV1 -
 B&AEF, 79-6857
 L E5 B666TJ A1 DQ E1 FY1&2VQ OQ
 79-6631
 L E5 B666TTT&J E1 FQ FIUUI OQ
 79-6856
 L E5 B666TTT&J E1 FQ OQ, 79-6819
 79-6852, 79-6853, 79-7137
 L E6 B666J, 79-6861
 L E6 D6656 1A T&&T&T&J PQ R1
 79-6828

L E6 D6656 1A T&&T&T&J R1, 79-6679
 79-6687, 79-6744, 79-6746, 79-6761
 79-6808, 79-6819, 79-6821, 79-6822
 79-6823, 79-6824, 79-6825, 79-6826
 79-6827, 79-6828, 79-6830, 79-6883
 79-6907, 79-7066, 79-7070, 79-7080
 79-7082
 L E6 D6656 1A T&T&T&T&J KQ LQ R1
 79-6828
 L E6 D6656 1A TT&T&T&J FQ GQ R1
 79-6808
 L E6 D6656 1A TT&T&T&J HQ IQ R1
 79-6808, 79-6828
 L G6 D6 B666J, 79-6807, 79-6819
 L545 B4 C5 D 4ABCE J DVTJ-/G 10
 79-6782
 L6TJ AMVMSWR DV1, 79-6720
 L6UTJ A1 A1 BIUIY1&UZUIY1VQ&1
 C1 -T, 79-6843, 79-6889
 L6UTJ A1 BL/UIY1&U2/ 2Q C1 C1 -T
 79-6842, 79-6843, 79-6900
 L64TJ A1 BIUIY&U2UIY&U2OV1 C1
 C1, 79-6843, 79-6853
 L66J BOVM1, 79-6812
 L66J BSWQ ENUN- BL66J CQ DSWQ
 HSWQ &-NA- 3, 79-6791
 L66J BZ GZ, 79-6772
 L66J CZ, 79-6771, 79-6822
 L666 B6 2AB PJ, 79-6815
 ONNR&R, 79-6730
 ONN1, 79-6732
 ONN1&VM1, 79-6867
 ONN1&VO2, 79-6700, 79-6812
 ONN1&Y1&R, 79-6742
 ONN1&1, 79-6608, 79-6698, 79-6704
 79-6721, 79-6722, 79-6734, 79-6863
 79-6864
 ONN1&1OV1, 79-6865
 ONN1&1R, 79-6742
 ONN1&2R, 79-6742
 ONN1V1&1V1, 79-6728
 ONN1YQ1&1V1, 79-6726
 ONN1YQ1&1YQ1, 79-6721, 79-6726
 79-6727
 ONN2&VO2, 79-6701
 ONN2&1U1, 79-6610
 ONN2&2, 79-6609, 79-6633, 79-6678
 79-6722, 79-6724, 79-6725, 79-6812
 79-6862, 79-7123
 ONN2GVM2G, 79-7155
 ONN2Q&2Q, 79-6611, 79-6695, 79-6696
 79-6734
 ONN2U1&2U1, 79-6610
 ONN3&1V1, 79-7125
 ONN3&1Y1&OV1, 79-7125
 ONN3&3, 79-6694, 79-6721, 79-6729
 ONN4&2, 79-6729

ONN4&4, 79-6721, 79-6733
 ONN5&VO2, 79-6701
 ONI&UNI, 79-6768, 79-6860
 ONI&UNIOVI, 79-6675, 79-6768
 OO, 79-6871, 79-6894
 OVI & 4-PB-, 79-6646, 79-6689
 QR BE, 79-6746
 QR BG DG FG, 79-6747
 QR BQ CQ, 79-6784
 QR BQ DYQIMY1&1 -L, 79-6800
 79-6819
 QR DE, 79-6746
 QR DMV1, 79-6616
 QR DV2, 79-6851
 QR DYU2&YU2&R DQ, 79-6851, 79-7174
 QR DY2& 2, 79-7174
 QR DY2& 2U, 79-6602, 79-6619, 79-6620
 79-6679, 79-6703, 79-6846, 79-6847
 79-6849, 79-6850, 79-6851, 79-6852
 79-7011, 79-7174
 QR-/G 5, 79-6774
 QVYZIOVIUNN &10/11, 79-6683
 QVYZIR CQ DQ -L, 79-7195
 QVYZIR DN2G2G -L, 79-7155
 QVYZ2UQ, 79-6737
 QVIMYZUM, 79-6706
 QVIOR BG DG EG, 79-6677, 79-6774
 QVISIVQ, 79-6739
 QVIXQ1&2Q, 79-7197
 QY1&1N3&NO, 79-6721
 Q1YG, 79-6666
 Q2, 79-6640, 79-6661, 79-6761, 79-7181
 Q2K &Q, 79-6683
 Q4N4&NO, 79-6721, 79-6731, 79-6732
 79-6733, 79-6849
 R, 79-6761, 79-7176
 RNUNR, 79-6766
 SHIYVQZ, 79-6707
 SN1&VN1&1, 79-6711
 SUYZMR, 79-6718
 T B666 GK JK&T&J &9/19 &12/22
 79-6758
 T C566 DO LVOJ BO1, 79-6071, 79-6287
 79-6359, 79-6872
 T C666 BN ISJ EG B3- AT6N DNTJ
 D2Q, 79-7198
 T C666 BO EV INJ D1 FZ N1 G-
 K-/ VM- OT5-16- AN FVN IVN LVO
 PVM SVTJ G1 J1 KY NI
 RY 2, 79-7192, 79-7194
 T D6 B6666 2AB JV OV T&T&T&J
 79-6836
 T D6 B6666 2AB JV QV T&T&T&J
 79-6836
 T E3 D5 C555 A D- FO KUTJ AG AG BG
 JG KG LG, 79-6609
 T E3 D6 B6666 2AB U FOTT&&&J HQ
 IQ 79-6815, 79-6834

T F5 C6 B655 DOV GV OO QO
 RUT&&TTJ LO1, 79-6609, 79-6787
 79-6788, 79-6790, 79-6791, 79-6859
 T3NTJ A- 3PST3NTJ A- 3PS, 79-6785
 T3OTJ B- 2, 79-6670, 79-6744
 T3OTJ B1, 79-6744
 T3OTJ B1G, 79-6744
 T4OVTJ, 79-6700
 T45 ANV ESTJ CMVIR& F1 F1 GVQ
 79-6823
 T5N CNJ A1 B1 ENW, 79-6735
 T5N CSJ BMVM2 ENW, 79-6713
 T5N CSJ DNW B- CT5MVTJ, 79-6868
 T5NTJ ANO, 79-6612, 79-6734
 T5OJ BNW E- ET5N CSJ BMVH
 79-6733
 T5OJ BYVZU1- BT5OJ ENW, 79-6690
 T5OV EHJ CQ DQ EYQ1Q, 79-6681
 T5SW CUTJ, 79-6778
 T55 AN CUTJ DIOVXQXQ&&YO1
 FOVYU2, 79-6776
 T55 AN CUTJ DIOVXQY&&YO1 FQ
 79-6776
 T56 BKJ C1 D1VQ FO1 BR OVG&
 79-6795, 79-6803
 T56 BM DN FNVNVJ F1 H1, 79-6876
 T56 BN DN FMVMVJ B1 GUM, 79-6704
 79-6709, 79-6865
 T56 BN DN FMVMVJ GUM D- B5SOTJ
 CQ DQ EIQ, 79-6740
 T56 BN DN FN HNJ IZ D- B5SOTJ CQ
 DQ EIQ -A&CD, 79-6740
 T56 BN DN FNVNVJ B1 F1 H1, 79-6876
 79-6891, 79-7177
 T56 BO DO CHJ G2U1, 79-6609, 79-6614
 79-6748
 T56 BOXVJ FO1 HO1 IG C-& DL6V DX
 BUTJ CO1 EI, 79-6785
 T56 BVOVJ, 79-6762
 T6KJ A D- 2 &G &G &3/14 &3/17
 79-6698, 79-6758
 T6MPOTJ BO BN2G2G, 79-6686
 79-6744, 79-6771, 79-6866
 T6MPOTJ BUO BN2G2G FOQ, 79-6601
 T6MVMVJ EF, 79-6738
 T6N CNJ BY1&1 DOPS&O2&O2 F1
 79-6764
 T6N DOTJ ANO, 79-6612
 T6N DOTJ ANO C1 EI, 79-6612, 79-6745
 79-7125
 T6NJ C- B5SNTJ ANO, 79-6611
 T6NJ DVMZ, 79-6616
 T6NTJ ANO, 79-6612, 79-6721
 T6NTJ ANO C1 EI, 79-6745
 T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C
 79-6893
 T6VMVMV FHJ F2 FR, 79-6687, 79-6742
 79-6746, 79-6819
 T6VMVMV FHJ F2 FR &-NA-, 79-6675
 T6VMVTJ E1YQ- BL6VTJ D1 F1
 79-6821, 79-6985, 79-7194

T656 BN GN LNJ CZ I1, 79-6737
 T66 BM DN FN HNJ IS- ET5N ONJ
 DNW, 79-6781
 T66 BN DN GN JNJ CZ EZ H1N1&R
 DVMYVQ2VQ *L L DX
 79-6783
 T66 BNJ BO ENW, 79-6743, 79-6744
 T66 BNJ EMY&3N2&2 IG, 79-6876
 T66 BNNNVJ DISPS&O1&O1, 79-6777
 T666 BO IO T&&J EG FG LG MG
 79-6773, 79-6813, 79-6819
 T7NTJ ANO, 79-6612, 79-6721
 T8NTJ ANO, 79-6612
 VHH, 79-6742
 VHR, 79-6742
 VH1, 79-6661, 79-6678
 VH1G, 79-6739
 VH1YQYQYQ1Q -BAA -D, 79-6941
 WNMVUM&N1&NO, 79-6700, 79-6866
 79-7044, 79-7129
 WNR DO- 3PO, 79-6681
 WNR DOPS&O1&O1, 79-6741
 WNR DOPS&O2&O2, 79-6765
 WNR DYQY1QMUYGG -DL, 79-6622
 79-6757
 WN6, 79-6693
 WSO&NUNR DN1&1 &-NA-, 79-6656
 WS1&O1, 79-6700
 WS1&O2, 79-6649, 79-6700, 79-6899
 79-7044, 79-7187
 WS1&O3, 79-3725
 WS1&O4, 79-6700
 ZR BO1 EI, 79-6755
 ZR B1 &GH, 79-6752
 ZR B1 DR B1, 79-6768
 ZR CG F1, 79-6751
 ZR DR, 79-6768
 ZR DSWR DZ, 79-6613
 ZR XNW XNW, 79-6729
 ZVM2, 79-6703
 ZVN1&NO, 79-6607, 79-6618, 79-6700
 79-6704, 79-6705, 79-6707, 79-6708
 79-6709, 79-6710, 79-6867, 79-6999
 ZVN2&NO, 79-6607, 79-6608, 79-6609
 79-6618, 79-6651, 79-6703, 79-6707
 79-6712, 79-6714, 79-6715, 79-6716
 ZVN3&NO, 79-6607, 79-6707
 ZVN4&NO, 79-6607
 ZVO2, 79-6633, 79-6698, 79-6699
 1&Y1&3Y1&3Y1&3Y1&1, 79-6672
 1MM1, 79-6631, 79-6673, 79-6674
 79-6675, 79-6768
 1N1&NUNR, 79-6709
 1N1&R DNUNR C1, 79-6756, 79-6757
 1N1&R DIUIR, 79-6848
 1N1&R DIUIR -T, 79-6848
 1OVR DVO1, 79-6749

1R, 79-6761

1SX1UNOVM1&1&1, 79-6780, 79-6812

1U2R DO1, 79-6614

1VOR BVQ, 79-6795

1X1&1&R BQ CX1&1&1 E1, 79-6674
79-6698, 79-6699, 79-6753

1Y&MVR D1MM1, 79-6243, 79-6244
79-6299, 79-6750

1Y&OPO&FOY1&1, 79-6865

1Y1&1R BQ EO1, 79-6832

1Y1&1R CQ FO1, 79-6832

1Y1&1V1, 79-7165

2N2&VYGU2OPO&O1&O1, 79-6655

2N2&YUS&S1YGU1, 79-6702

2OR DMV1, 79-6615

2U1R BO1 DO1 EO1, 79-6614

2VXR&R&1Y&N1&1 &GH, 79-6671

2V1 79-7165

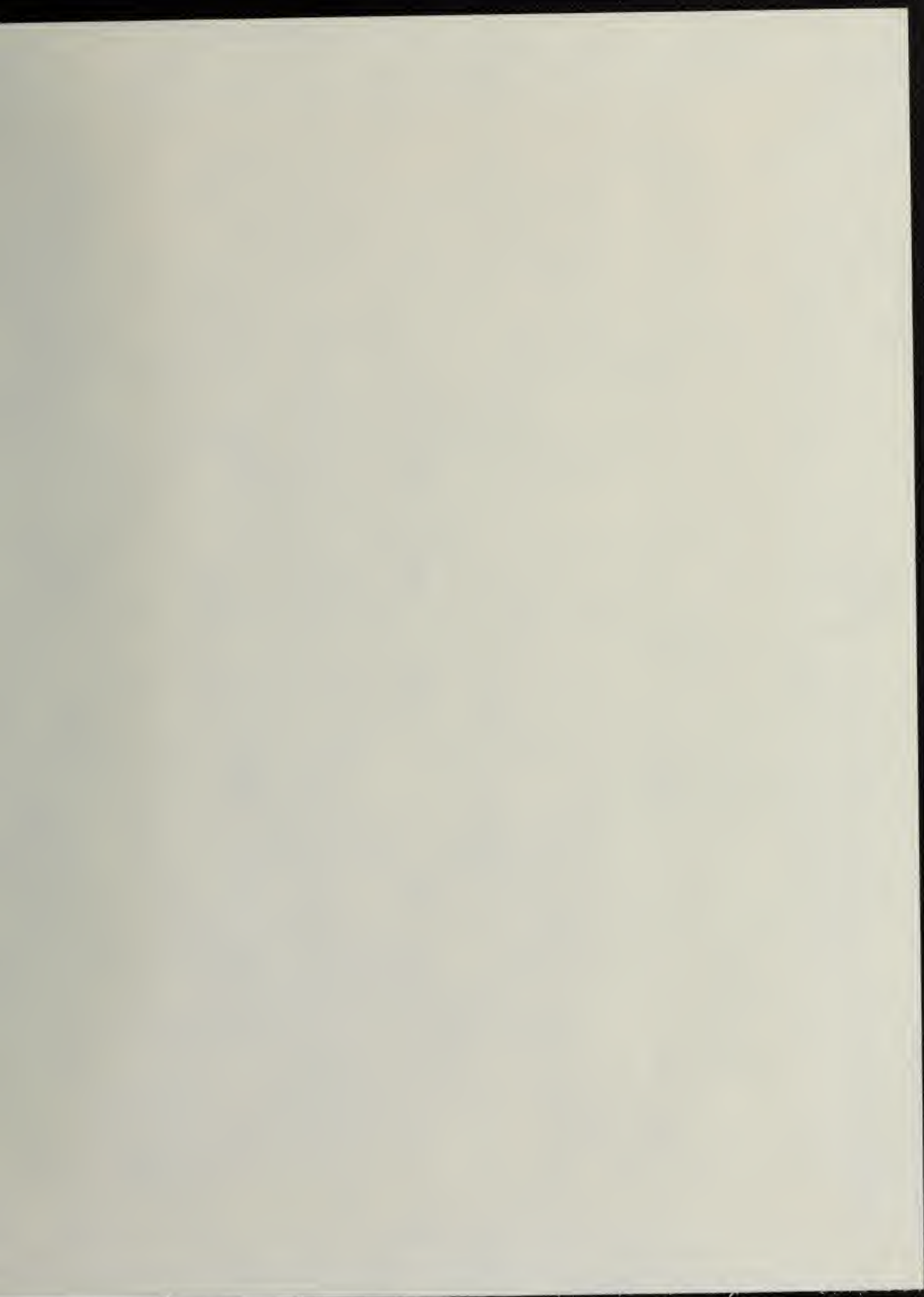
3XR&R&VO2N2&2 &GH, 79-6819

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